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Randomized, double-blind, placebo-controlled trial of Meriva® (curcuminoids) as a candidate chemoprevention agent for gastric carcinogenesis

Consortium Name: **Cancer Prevention Network (CPN) ****
Consortium Lead Investigator: Paul J. Limburg, M.D., M.P.H.
Professor of Medicine
Mayo Clinic College of Medicine
200 First Street, SW, Rochester, MN 55905
Telephone: 507-284-2511
Fax: 507-266-4371
E-mail: limburg.paul@mayo.edu

Organization: **University of Puerto Rico**
Protocol Co-Principal Investigator: Marcia Cruz-Correa, M.D., Ph.D. *
Associate Professor of Medicine & Biochemistry
NCI Institution code: PR008
P.O. Box 70344, PMB 371,
San Juan PR 00936-8344
Telephone: 787-772-8300
Fax: 787-522-3282
E-mail address: marcia.cruz1@upr.edu

Organization: **University of Alabama at Birmingham****
Protocol Co-Principal Investigator: Douglas Morgan, M.D, M.P.H. FACG†
Professor of Medicine and Epidemiology
1720 2nd Avenue South
Birmingham, AL 35294-0111
Telephone: 205-934-5266
E-mail address: drmorgan@uabmc.edu

Organization: **Mayo Clinic****
Protocol Statistician: Nathan R. Foster, M.S. †
200 First Street, SW, Rochester, MN 55905
Telephone: 507-284-5051
Fax: 507-266-2477
E-mail: foster.nathan@mayo.edu

* Investigator having NCI responsibility for this protocol
† Study Contributor(s) not responsible for patient care
** Administrative/Non-accruing site. No participant accrual occurs at this site

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Facilities at which visits and procedures will take place

University of Puerto Rico **Puerto Rico Clinical and Translational** Research Consortium 1st Floor University Hospital Medical Sciences Campus P.O. Box 365067 San Juan, PR 00936-5067	**Hospital de Occidente** Ministry of Health Barrio El Calvario Santa Rosa de Copan, Honduras
Oncology Hospital Dr. Isaac Gonzalez **Barrio Monacillos, Medical Center, Rio Piedras** P.O. Box 191811 San Juan PR 00919-1811	

Investigators and Collaborators

Keila L. Rivera Román MD, FCAP, FASCP† **University of Puerto Rico** Assistant Professor Sub-specialist in Molecular Genetic Pathology Dept of Pathology and Laboratory Medicine Lab B342, 343 University of Puerto Rico Medical Sciences Campus Phone: 787-758-2525 x.2385, 1331 Email: keila.rivera11@upr.edu	**Ricardo Dominguez, M.D.** **Hospital de Occidente, Honduras** NCI Institution code: 24002 Chief of Gastroenterology and Endoscopy Santa Rosa de Copan, Honduras Telephone: 504-2-26620107 Fax: 504-2-33922412 Email: ricardo.l.dominguez@vanderbilt.edu
Eleazar E. Montalvan, M.D. **Hospital de Occidente, Honduras** Telephone: 504-3392-2412 Fax: 504-2-33922412 Email: eleazar.e.montalvan@vanderbilt.edu	

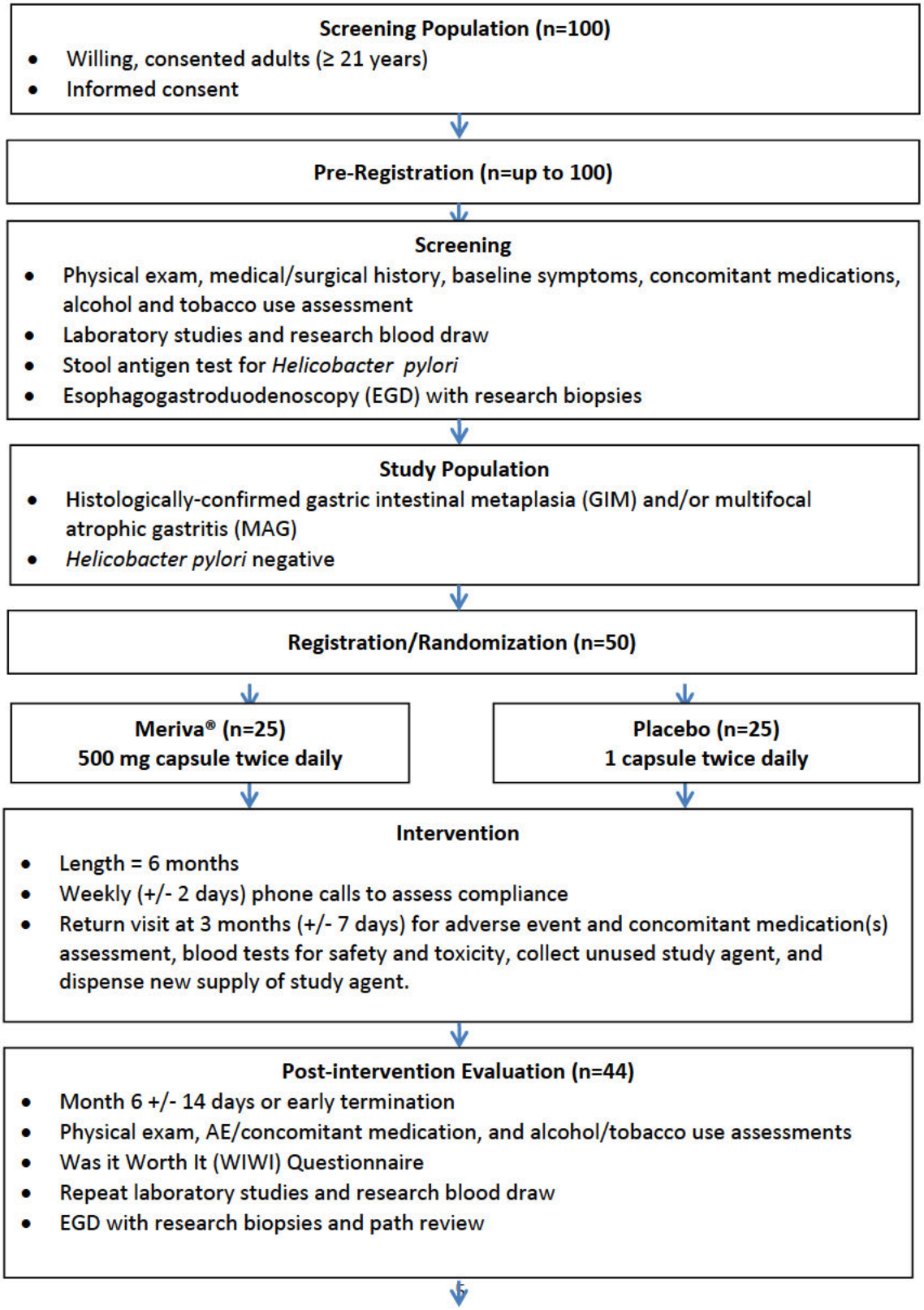
Sara M. Gorbea Gonzalez, MT, CHS **Department of Pathology and Laboratory Medicine** **Medical Sciences Campus, UPR** **General Supervisor**, Laboratorio de Inmunología y Enfermedades Infecciosas Departamento de Patología y Medicina de Laboratorio, Universidad de Puerto Rico Recinto de Ciencias Médicas, PO Box 365067 San Juan PR 00936-5067 Tel. 787-766-0728 Fax 787-754-0710 e-mail: sara.gorbea@upr.edu	**Maria Marcos, MD** **Professor of Medicine** **Department of Pathology & Laboratory Medicine** University of Puerto Rico Medical Sciences Campus Phone: 787-758-2525 x 2385, 1331 Email: Maria.marcos@upr.edu
Victor L. Carlo, M.D. **University of Puerto Rico** Telephone: 787-620-8716 Fax: 787-522-3282 Email: victor.carlo@upr.edu	**Priscilla Magno Pagatzaurtundua, M.D.** **University of Puerto Rico** Telephone: 787-344-3775 Fax: 787-522-3282 Email: Priscilla.magno@upr.edu
Lemuel F. Melecio Rodriguez, M.D. **University of Puerto Rico** Telephone: 787-299-9504 Fax: 787-522-3282 Email: lemuel.melecio1@upr.edu	**Irene Villamil Sanchez, M.D.** **University of Puerto Rico** Telephone: 787-632-4575 Fax: 787-522-3282 Email: irene.villamil1@upr.edu

Contacts

Questions:	Contact Name:
Test schedule, Intervention Delays/Interruptions/Adjustments Adverse events	**Jessica Hernandez-Marrero, R.N., MSN, CON** *Lead Study Coordinator* Phone: 787-772-8300, Ext 1158 Email: jessica.hernandez8@upr.edu
Serious Adverse Event reporting	**See Protocol Section 11.2**
Subject eligibility, Forms completion, paraffin-embedded biospecimens	**April Felt** CPN *Research Base* Data Manager and Pathology Coordinator Phone: 507-538-0268 Fax: 507-266-3722 E-mail: felt.april@mayo.edu
CPN Lead Site Coordinator	**Colleen Akerley** CPN *Research Base* Senior Program Coordinator Phone: 507-284-2180 Fax: 507-266-4371 E-mail: akerley.colleen@mayo.edu
Protocol Development	**Sharon Kaufman** CPN *Research Base* Senior Research Protocol Specialist Phone: 507-293-1605 Fax: 507-266-4371 E-mail: kaufman.sharon@mayo.edu
Regulatory Administrative	**Patty Simonson** CPN *Research Base* Regulatory Affairs Specialist Phone: 507-266-2218 Fax: 507-266-4371 E-mail: Simonson.patricia1@mayo.edu
All other administrative issues	**CPN Operations Office (8:00-3:00 Central Time)** Phone: 507-266-2218 or 293-1605; Fax: 507-266-4371 Email: cancerpreventionnetwork@mayo.edu
Pre-Registration and Registration/Randomization Unblinding of Study Agents	**CPN Registration Office (8:00-4:30 Central Time)** Phone: 507-284-4130; Fax: 507-284-0885 E-mail: random01@mayo.edu
Monitoring Education	**Anne Holland** CPN *Research Base* Compliance Coordinator Phone: 507-293-7795 Fax: 507-284-1902 Email: holland.anne@mayo.edu
All other biospecimens Biospecimens collection and shipment	**Roxann Neumann** CPN *Research Base* Biospecimen Resource Manager Phone: 507-538-0602 E-mail: Neumann.roxann@mayo.edu

Randomized, double-blind, placebo-controlled trial of Meriva® (curcuminoids) as a candidate chemoprevention agent for gastric carcinogenesis

SCHEMA



Follow Up

- Phone call at Month 7 (+/- 14 days) or 30 days (+/- 14 days) after the Post-Intervention Evaluation (in the event of early termination) to assess AEs and concomitant medications

Endpoints

- Primary: To compare the absolute change in Interleukin-1beta (IL-1β) cytokine levels (measured by Luminex Assay) in the gastric mucosa from baseline to 6 months among participants randomly assigned to receive either Meriva-500® or placebo
- Secondary Endpoints (prioritized order):
  - Safety: To determine the safety and tolerability of Meriva® versus placebo
  - Change in Histology Gastric Score (HGS) from baseline to 6 months for Meriva® versus placebo
  - In participants with precancerous gastric lesions, to determine the effect of Meriva® versus placebo on the following endpoints (comparing the change from baseline to 6 months):
    - Additional gastric mucosal cytokine/chemokine levels (interleukin 9 [IL-8], tumor necrosis factor alpha [TNFα], and inducible protein 10 [IP-10] quantified by Luminex Assay);
    - Gastric mucosal DNA damage, as assessed by immunohistochemistry (IHC), of the biomarkers 8-hydroxy-2' –deoxyguanosine (8-OHdG) and phosphorylated subtype of histone H2A [H2AX];
    - Associations between proinflammatory cytokine genotype status (IL-1β, IL-8, and TNFα single nucleotide polymorphisms [SNPs] characterized at baseline) and the above outcomes. These will be considered exploratory analyses.

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1. OBJECTIVES

1.1 Primary Objective

To compare the change in gastric mucosal Interleukin 1beta (IL-1β) cytokine level, quantified by Luminex assay technology, after a 6 month intervention in participants randomly assigned to the Meriva® (curcuminoids) versus placebo arms.

1.2 Secondary Objectives

After a 6-month intervention in participants randomly assigned to the Meriva® versus placebo arms:

- To determine the safety and tolerability of Meriva® versus placebo;
- To compare changes in Histology Gastric Score (HGS) from baseline to 6 months for Meriva® versus placebo;
- To compare changes in additional gastric mucosal cytokine/chemokine levels (Interleukin 8 [IL-8], tumor necrosis factor alpha [TNFα], and inducible protein 10 [IP-10]; quantified by Luminex assay);
- To compare changes in gastric mucosal DNA damage as assessed by Immunohistochemistry (IHC), of the biomarkers 8-hydroxy-2' –deoxyguanosine (8-OHdG) and phosphorylated subtype of histone H2A (H2AX);
- To explore associations between proinflammatory cytokine genotype status (IL-1β, IL-8, and TNFα single nucleotide polymorphisms [SNPs]; characterized at baseline) and the above outcomes.

2. BACKGROUND

2.1 Gastric Cancer

Global Burden: Gastric cancer (GC) is the 4th most common incident cancer and the 2nd leading cause of cancer death worldwide.[1] Approximately 990,000 people are diagnosed with GC worldwide, of whom close to 75% die from this disease.[2] GC also is responsible for one of the highest cancer burdens, as determined by disability-adjusted life years lost.[3] Despite the overall decrease in the incidence of GC since the 1930s, the annual global burden of cancer is projected to double by 2030 to 22.2 million incident cases and 13.1 million deaths, with over two-thirds of the burden in resource-limited nations.[4, 5] In the US, the American Cancer Society estimates that in 2015 24,590 new cases of GC will be diagnosed and approximately 10,720 individuals will die from this type of cancer.[6] The average risk that a person will develop GC in his/her lifetime is about 1 in 111, with the risk being 2 to 3-fold higher in men than women. However, GC incidence rates vary dramatically across different countries and are higher in less developed countries.[2] GC is more common in East Asia, Southern and Eastern Europe, and South and Central America whereas the lowest incidence rates are observed in Africa and North America.[7] Although nearly 60% of the new GC cases are diagnosed in Asia,[8] significantly better outcomes

have been reported among Asian individuals compared to those diagnosed in Western countries.[9] Five-year GC survival rates are 40% lower in the US and Europe compared to Japan.[10]

Risk Factors. The risk factors for the development of gastric cancer include: male sex, older age, *Helicobacter pylori* status, tobacco smoking, diet, living in places with high altitude, low socioeconomic status, and being part of the Asian, Hispanic, and African American communities.[11, 12]

Racial/ethnic GC Disparities. Although the number of deaths from GC has been steadily declining, significant geographical and racial/ethnic health disparities in GC incidence and mortality continue to be observed. The observed decline in GC incidence has been occurring more in tumors of the non-cardia, which are mostly attributable to *H. pylori,* smoking, and high salt diets.[13] Asians, Hispanics and Blacks in the U.S. have been reported to have a higher proportion of distal GC (tumors in the body, antrum, and pylorus) compared to Whites, which are most commonly diagnosed with proximal GC (tumors in the cardia and fundus).[14] A significantly higher incidence of GC has been observed among Asians, followed by Blacks and Hispanics compared to Whites.[12, 15, 16] Interestingly, GC incidence is similar in all racial/ethnic groups in the U.S. until age 60–64, where Asian incidence rates increase dramatically. From 1992 to 2009, overall 3-year survival was highest among Asians (26%), followed by Blacks, Hispanics, and Whites, which had comparable survival rates (~19%).[12] Geographical differences in the incidence of GC have also been observed among regions in the U.S., with the highest incidence reported in the West followed by the Northeast.[12]

The reasons for the geographic and racial/ethnic GC disparities remain incompletely understood and may be due to a combination of factors which may include barriers to healthcare, environmental factors, and/or genetic factors.[17] Latin America has a significant GC burden, with a concentration of disease in the mountainous regions of the Pacific littoral zone,[18-20] where the mortality-to-incidence ratio is extremely high at 0.82. In the U.S., GC represents a marked health disparity where non-whites, including Hispanics, have nearly 2-fold higher incidence rates, for reasons that remain largely uninvestigated.[15, 16] Hispanics are projected to comprise 25% of the U.S. population by 2040-2050, and represent a large at-risk population, particularly immigrants from high incidence areas, such as Central America. However, when evaluating cancer susceptibility factors in the U.S., Hispanics from different populations are usually grouped together.

A comprehensive understanding of the factors affecting GC disparities will help to target educational programs to individuals at higher risk of GC and to develop prevention strategies, including chemoprevention, to reduce the disease burden across all racial/ethnic groups.

2.2 Meriva®/curcuminoids

Curcumin is a phenolic antioxidant compound derived from the rhizome of the plant *Curcuma longa*. Curcumin has long been used as a spice in India and other parts of Asia and is considered a safe food additive. This bioflavonoid is a potent inhibitor of arachidonic acid metabolism, and blocks both lipoxygenase and cyclooxygenase activity in the intestinal mucosa. Curcumin exerts a variety of additional immunomodulatory and antioxidant effects and is thought to have broad chemopreventive potential through a variety of molecular mechanisms and cellular pathways, as recently reviewed.[21]

Meriva® is a unique curcumin product available to the investigative team by Thorne Research (Dover, ID). The overall curcuminoid absorption from the Meriva® formulation is about 29-fold higher than that of the corresponding unformulated curcuminoid mixture.[22] The improved absorption and enhanced plasma curcuminoid profile make Meriva® an attractive candidate agent for chemoprevention trials.

2.3 Rationale

Gastric intestinal metaplasia and chemoprevention: Gastric precancerous lesions, such as gastric intestinal metaplasia (GIM) are prevalent both in high and low incidence regions of the world. GIM is the replacement of gastric mucosa by an epithelium that histologically resembles intestinal mucosa and is a key event in gastric carcinogenesis. The prevalence of GIM varies depending on the rate of *H. pylori* infections in the population.[23] Intestinal metaplasia is present in approximately 20% of all gastric biopsies,[24] but up to 10% of patients with GIM will progress to GC.[25] Current guidelines for symptomatic individuals with extensive GIM recommend endoscopic surveillance every 3 years.[26] Unfortunately, the limited efficacy of *H. pylori* eradication strategies in patients with GIM emphasizes the need for other pharmacologic intervention to prevent GC progression.[27, 28] *H. pylori* induced chronic gastritis increases the level of COX-2 expression in the stomach mucosa. Enhanced expression of COX-2 is also observed in intestinal metaplasia and dysplasia.[29] NSAID and aspirin use have been examined as GC chemoprevention agents. Use of these agents has been associated with a reduction in the odds of distal gastric cancer.[30, 31]

Curcumin is a phenolic antioxidant compound derived from the plant *Curcuma longa* that is used as a spice in India and has been shown to block both lipoxygenase and cyclooxygenase activity in the intestinal mucosa.[32, 33] Curcumin has several anticarcinogenic actions including anti-inflammatory and antioxidant properties.[34] With the high GC mortality-to-incidence ratio and the lack of routine screening methods available for asymptomatic individuals, the management of GC remains a challenge and warrants further investigations to more fully understand the biologic basis of progression and to develop chemopreventive strategies for individuals at increased risk.

Population Health Perspective: The Central America Four (CA4) nations (Honduras, El Salvador, Guatemala, and Nicaragua) form the core low/middle income (LMIC) region in the western hemisphere. The CA4 is unified by its geography, history, language, and culture. These countries opened their borders in 2006, and are in transition towards a union of their health systems and infrastructures. A regional approach to cancer control is essential, and cancer capacity-building is imperative. The CA4 population is nearly 35 million, with an estimated immigrant population of 4-5 million, making it unique for cancer control among global LMICs from a U.S. perspective, given the burgeoning U.S. Hispanic population. The Honduras-Puerto Rico partnership in gastric cancer truly provides a unique and powerful platform for chemoprevention and clinical translational studies in Hispanic populations, and the two proposed study sites have characteristics that are appeasing for the current study design, which include:

- Puerto Rico and Central America (Honduras) have a high prevalence of GIM (detected in approximately 20% of asymptomatic patients in the Endoscopy Clinics). However, the sites have different gastric cancer incidence rates,[2] which will be noted by the use of stratification factors.
- In both Puerto Rico and Honduras, curcumin is not part of the local diet, nor is it readily available. Therefore, dietary curcumin will not be a confounder in the proposed study setting.

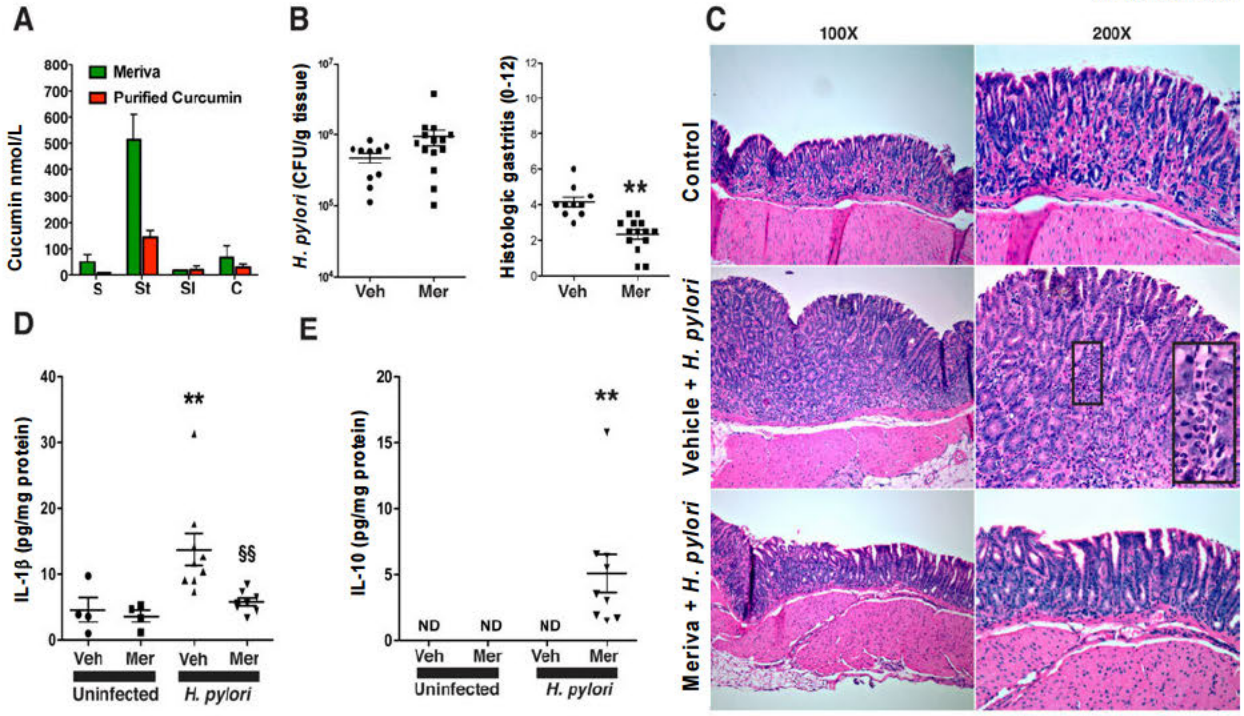

Figure 1. Meriva reduces gastritis and modulates cytokine responses in murine *H. pylori* infection.

Findings:

A. Curcumin levels were measured by mass spectrometry in different sites; S, serum; ST, Stomach; SI, small intestine; and C, colon.

B: Quantification of *H. pylori* colonization and histologic gastritis. Veh, vehicle (equivalent to placebo); Mer, Meriva.

C: Representative H&E staining of mouse stomach tissues, showing reduced mucosal thickening and inflammatory cell infiltration with Meriva.

D and **E:** Cytokine levels measured in stomach tissue lysates by the Luminex assay (multiplex bead array). Note in panels D and E, "uninfected" implies never-infected in the mouse model; in human populations, nearly all subjects with IM have had chronic *H. pylori* infection, but may not have measurable active infection in mid-adulthood. Note that IL-10 is a recognized anti-inflammatory cytokine, demonstrating a potential protective effect from Meriva in panel E.

Supporting Data for Biomarker Endpoints (from mouse models): Findings from recent animal model experiments conducted at Vanderbilt are highlighted in Figure 1 (above).

Panel A: Mice were gavaged with purified curcumin or the equivalent concentration of Meriva® (150 nM) and were sacrificed 1 hour later.

Panels B-E: Young adult mice were continuously fed a diet containing either Vehicle or Meriva® (2% curcumin by weight). Mice were infected with the *H. pylori* SS1 strain. Four months post-inoculation, they were sacrificed and endpoints were measured. (Data provided courtesy of Dr. Rupesh Chaturvedi, former post-doctoral member of the Vanderbilt Wilson Lab. During this period, Dr. Chaturvedi was an NIH K01 Awardee, focused on curcumin and gastric cancer.)

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline and Month 6, to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

General Overview: Chronic multifocal atrophic gastritis (MAG) and gastric intestinal metaplasia (GIM) are established precancerous lesions. Participants with MAG, GIM, or both will be identified or confirmed at the baseline upper endoscopy. Willing, eligible trial participants will then be registered and randomized to receive either Meriva® 1000 mg (one 500mg capsule twice per day for a total curcuminoid intake of 200 mg/day) or matching placebo (1 capsule twice per day). A follow-up upper endoscopy will be performed at 6 months (See Schema). We anticipate that the majority of enrolled subjects will have GIM, which confers higher gastric cancer risk. Therefore, baseline histology will be used for stratification.

Screening and Baseline: At both the Puerto Rico and Honduras recruitment sites, potential study participants with a confirmed or suspected diagnosis of gastric MAG and/or GIM will be pre-selected using detailed clinical and research databases that are currently in place and have been demonstrated to be effective for recruitment purposes in other recent studies. Participants who meet the inclusion and exclusion criteria will undergo a comprehensive history and physical examination, alcohol and tobacco use assessments, eligibility/baseline blood testing, *H. pylori* stool antigen testing, research blood collection, and upper endoscopy with biopsies.

Randomization: Eligible participants will be randomized in a 1:1 fashion to 1000 mg Meriva® (one 500mg capsule twice per day, for a total of 200 mg curcuminoids/day) or matching placebo for a 6-month intervention period, using a dynamic allocation procedure called the Pocock-Simon[35] that balances marginal distributions of the stratification factors across defined intervention groups and has been shown to be able to accommodate a large number of factors (10-20) without difficulty.[36] The randomization will be stratified based on enrolling site (Honduras or Puerto Rico) and baseline gastric mucosal histologic diagnosis (MAG, GIM, or both). The study teams will make weekly phone calls to the participants, and participants will return at 3 months for the assessment of adverse events, blood tests for safety and toxicity, protocol compliance, and concomitant medication usage.

End of Intervention: Participants will return at 6 months for a physical exam; research blood collection, assessment of adverse events, protocol compliance, and concomitant medication

usage, follow-up alcohol and tobacco use assessments, completion of the Was It Worth It (WIWI) questionnaire, and upper endoscopy.

4. PARTICIPANT SELECTION

4.1 Pre-Registration Inclusion Criteria

4.1.1 Age ≥21 years. Because no dosing or adverse event data are currently available on the use of Meriva® in younger individuals, and because GIM and MAG are extremely uncommon in children, children are excluded from this study but will be eligible for future pediatric trials.[37]

4.1.2 Ability to understand and the willingness to sign a written informed consent document

4.1.3 Willingness to undergo screening tests and procedures

4.1.4 Willingness to provide blood and tissue samples for safety/toxicity monitoring and biomarker analyses

4.1 5 Willingness to avoid the use of curcumin or any over-the-counter or prescription medications containing curcumin or curcuminoids.

4.2 Pre-Registration Exclusion Criteria

4.2.1 History of other malignancy ≤ 2 years prior to the Registration/Randomization evaluation, with the exception of basal cell or squamous cell skin cancer

4.2.2 History of colorectal cancer. Exception: Individuals with Stage I or II colorectal cancer who have not received any chemotherapy.

4.2.3 Known diagnosis of HIV. Note: An HIV screening test does not have to be performed to evaluate this criterion.

4.2.4 History of gastric surgery

4.2.5 Receiving any other investigational agents.

4.2.6 Use of any anticoagulation medications, such as warfarin or Coumadin

4.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

4.2.8 Pregnant or breast feeding. Note: Pregnant women are excluded from this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Meriva®, breastfeeding should be discontinued if the mother is treated with Meriva®.

4.3 Registration/Randomization Inclusion Criteria

4.3.1 Histologically-confirmed chronic multifocal atrophic gastritis (MAG) and/or gastric intestinal metaplasia (GIM)

4.3.2 *Helicobacter pylori* negative, defined as negative stool antigen testing and negative histological examination.

4.3.3 ECOG performance status ≤1 (See Appendix A)

4.3.4 Participants must have normal organ and marrow function, defined as lab values (AST, ALT, Alkaline phosphatase, CBC [Platelets, Hemoglobin, WBC], BUN, Total bilirubin, Creatinine) within institutional limits of normal or judged to be not clinically significant by the investigator

4.3.5 Not pregnant or breast feeding. Note: The effects of Meriva® on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, individuals of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.4 Registration/Randomization Exclusion Criteria

4.4.1 Receiving any other investigational, anticoagulation, and/or chemotherapy agents

4.4.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Meriva®.

4.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.6 Recruitment and Retention Plan Summary

Site-specific recruitment, retention, and adherence (RR&A) plans will be submitted by each site as part of the regulatory packet required prior to site activation. In summary, at both the

Puerto Rico and Honduras recruitment sites, potential study participants with a confirmed or suspected diagnosis of gastric MAG and/or GIM will be pre-selected using detailed clinical and research databases that are currently in place and have been demonstrated to be effective for recruitment purposes in other recent studies.

Once on study, study participants will be contacted weekly to encourage and confirm compliance with study procedures. Site teams will document recruitment activities along with reasons for declining participation, not signing the informed consent document, screening failure, and/or discontinuing the study, the latter after registration/randomization. These data will be submitted to DCP, and the recruitment information will be reviewed by the CLO at least quarterly and compared with the plans and deadlines established among the site teams, the CLO, and NCI, DCP.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

- Meriva®/matching placebo capsules
- 1000 mg (two 500 mg capsules)/day
- Duration 180 days (+/- 14 days)

5.2 Meriva® Administration

- Meriva® will be self-administered.
- Study participants will be dispensed two bottles, each containing 100 capsules (Meriva® or placebo) at baseline and at the 3-month visit. Unused agent will be returned at the 3-month and 6-month visits.
- Participants will self-administer 1 capsule twice daily at approximately the same times each day.
- The dose of 1 capsule twice daily of Meriva® contains 200mg of total curcuminoids within relative standard deviation (RSD) of the given assay for determination.
- Although administration with food is not specified, potential gastrointestinal symptoms may be decreased by consuming the Meriva® with a meal.

5.3 Run-in Procedures

There will be no run-in procedures.

5.4 Contraindications

Meriva® may interfere with absorption and efficacy of the chemotherapy drug, irinotecan, captothecin, and cyclophosphamide. However, these individuals would not be eligible for this study.

There is a theoretical pharmcodynamic interaction with turmeric and anticoagulant medications. Therefore, participants on anticoagulant therapy will be excluded.[38-41]

Curcumin could theoretically inhibit CYP29C and CYP3A4. Thus, individuals taking medications considered to be sensitive substrates for either of these will be monitored carefully.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g*., biopsy) will also be included.

5.6 Dose Modification

In the event of adverse events that are at least possibly related to study agent, and/or at the discretion of the treating physician, a participant may discontinue study agent for a period of one week. If the symptoms have returned to baseline, the participant may be rechallenged at the level of 500 mg once per day for one week, after which the participant can return to the full dose of 500 mg twice per day. If symptoms persist or worsen after the study agent holiday, the participant will be taken off study agent. Please see Sections 8.3 and 8.4 for definitions and details regarding data collection and submission.

If any participant using medications that are substrates of CYP2A9/3A4 develops side effects (Grade 2 or above), we will discontinue study agent for a period of one week. If the symptoms have returned to baseline, the participant may be rechallenged at the level of 500 mg once per day for one week, after which the participant can return to the full dose of 500 mg twice per day. If symptoms persist or worsen after the study agent holiday, the participant will be taken off study agent.

5.7 Adherence/Compliance

5.7.1 Compliance will be defined as a study participant having taken 75% of the required doses. Weekly phone calls will be implemented to increase likelihood that participants comply with study instructions.

5.7.2 Compliance will be determined by participant report (medication diary) and tablet count after review by the site study coordinator. Compliance will be defined as ingestion of ≥ 75% of the planned agent doses. The primary endpoint analysis will be based on the intent-to-treat principle, where all randomized patients that complete both the pre-intervention and post-intervention exams will be included. Secondary data analyses will include all randomized participants (i.e. adverse event analyses) or relevant subject subgroups (i.e. those who demonstrate ≥ 75% compliance with the study agents), as appropriate.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND # [redacted] NCI, Division of Cancer Prevention)

Curcumin derived from the tropical plant *Curcuma longa* has a long history of use as a dietary agent, food preservative, and in traditional Asian medicine. It has been used for centuries to treat biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis. The preventive and therapeutic properties of curcumin are associated with its antioxidant, anti-inflammatory, and anticancer properties. Extensive research over several decades has attempted to identify the molecular mechanisms of curcumin action. Curcumin modulates numerous molecular targets by altering their gene expression, signaling pathways, or through direct interaction. Curcumin regulates the expression of inflammatory cytokines (e.g., TNF, IL-1), enzymes (e.g., COX-2, LOX, MMP9, MAPK, mTOR, Akt), adhesion molecules (e.g., ELAM-1, ICAM-1, VCAM-1), and apoptosis related proteins (e.g., Bcl-2, caspases, DR, Fas).[32-34] Curcumin modulates the activity of several transcription factors (e.g., NFκB) and their signaling pathways. Based on its ability to affect multiple targets, curcumin has the potential for the prevention and treatment of various conditions, including osteoarthritis.

Meriva® is a botanical extract that contains curcuminoid phytosomes (phosphatidylcholine conjugates). Phytosome technology is a solid state dispersion of botanical into a phospholipid matrix (typically lecithin coming from non GM soy or from sunflower). Hence, it is a form of pre-formulation, designed to boost the bioavailability of botanical compounds. The aspect of this pre-formulation is typically a powder that can then be formulated in topical or oral finished dosage forms (typically tablets, hard and soft gelatin capsules). Lecithin acts as a surfactant at biological level and, contemporarily, decreases the self-aggregation tendency of compounds like polyphenols or triterpenes. The composition of the curcuminoid mixture will include total curcuminoid content of 20% ± 2%. Of that total percent, the individual composition will be as follows: curcumin (16.3-16.8%), demethoxycurcumin (2.0-2.5%) and bisdemethoxycurcumin (0.25-0.35%).

The formulation of Meriva® that will be used in this clinical trial will be Meriva-500 (as opposed to the sustained release formulation). The overall curcuminoid absorption from the Meriva-500 formulation is about 29-fold higher than that of the corresponding unformulated curcuminoid mixture.[22] The improved absorption and enhanced plasma curcuminoid profile make Meriva an attractive candidate for chemoprevention studies, with an ability to administer doses

significantly lower than unformulated curcuminoid mixtures. Indena S.p.A, will provide the Curcuma phospholipid, Meriva, and is conducting quality control analyses on the raw material as per their standard protocol. Thorne Research will verify identity and conduct microbiological assays prior to production using Thorne Research's in-house Quality Control laboratory. Results of all quality control testing will be reviewed and approved by Thorne Research Quality Control personnel prior to releasing the raw material for manufacture into a finished, encapsulated product.

The placebo used in this study will be manufactured by Thorne Research, Inc. It will be matching in terms of size and color. It will also be matched in terms of excipients such as soy lecithin to improve the likelihood that any effect seen in the active treatment arm is due solely to the curcuminoids.

6.2 Reported Adverse Events and Potential Risks

6.2.1 Adverse events reported to Thorne Research (via SafetyCall) from 6/1/2013 to 12/10/2015:

Total Number of Individuals Submitting Reports	**23**
Total Number of Symptoms Reported	**43**
GI-related symptoms	**24**
Skin, muscle, joint symptoms	**9**
Miscellaneous	**10**

Meriva® AE Risk			
Product	**Total Number of Individuals Submitting Reports**	**Reports per Bottle**	**Reports per Serving**
Meriva-SR (120s)	**12**	1 in 20,331	1 in 1,219,860
Meriva 500 (120s)	**7**	1 in 17,976	1 in 1,078,560
Meriva 500 (60s)	**4**	1 in 15,780	1 in 476,393
Total	**23**	1 in 18,823	1 in 1,047,040

6.2.2 Summary of adverse events reported from clinical trials involving Meriva® or curcumin:

In a study of Meriva® for symptomatic primary osteoarthritis (OA), all of the OA symptoms improved in the active group as compared to a placebo group, and there were no reports of liver or kidney toxicity or other adverse events.[42, 43] Curcumin-phospholipid formulations studies in central serous chorioretinopathy, chronic anterior uveitis, benign prostatic hyperplasia, and pre-surgical carpal tunnel syndrome noted few, if any, adverse events. The

exact adverse events were not specified.[44-47] A report of Meriva for the reduction of serum IL-22 levels in patients with psoriasis vulgaris noted 3 adverse event reports among the individuals on the active treatment arm, including diarrhea and diarrhea with fever, but none were attributed to study intervention.[48] A study of curcumin for pediatric inflammatory bowel disease noted minimal reports of adverse events, none of which required dose de-escalation and none of which were felt to be related to curcumin.[49]

Regarding utilization of doses higher than in the present study, a dose of 6000 mg curcuminoids/day was well tolerated with the reports of side effects being similar between the active treatment and placebo groups in a study of curcuminoids for the reduction of oral lichen planus.[50] One systematic review of more than 60 completed studies of some form of curcumin, as well as a meta-analysis of randomized controlled trials for a variety of cancer and pre-cancerous conditions, noted few reported adverse events even at doses of up to 8000 mg/day curcuminoids.[51, 52] Sharma, et al. reported on a clinical trial in advanced, refractory colorectal cancer involving 0.45 to 3.6 g daily curcumin in which there were 2 reports of diarrhea (Grade 2), one report of nausea (Grade 2), 4 reports of increases in alkaline phosphatase (Grades 1 and 2) and 4 reports of increased lactate dehydrogenase (Grade 1). Dose limiting toxicities were not observed.[53] Dose-escalation studies indicate relative safety of curcumin at doses as high as 12 grams per day for 3 months.[54]

Possible Side Effects of Meriva®*:

Rare, Some May Be Serious **In 100 people receiving Meriva, 3 or fewer may have:**
• Loose stool (diarrhea) • Stomach ache • Feeling sick to your stomach (nausea) • Muscle pain (myalgia) • Joint pain (arthralgia) • Skin discomfort

* Meriva® Investigator's Brochure, 12/06/2016

6.3 Availability

Meriva® is an investigational agent supplied to investigators by Thorne Research through a collaborative agreement with NCI, Division of Cancer Prevention (DCP) (see Section 12.7).

At baseline and at the 3-month visit, participants will be provided with two bottles, each containing 100 capsules (500 mg per capsule) of Meriva® or matching placebo.

6.4 Agent Distribution

Agent will be shipped from Thorne Research to MRIGlobal for distribution to participating organizations.

Agents will only be released by MRIGlobal after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each Organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham, MRIGlobal, DCP Chemoprevention Agent Repository
1222 Ozark Street, North Kansas City, MO 64116
Phone: 816-360-3805
FAX: 816-753-5359
Email: NCI.DCP@mriglobal.org
Emergency telephone: 816-360-3800

6.5 Agent Accountability

The Site Principal Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility will be delegated to appropriately trained and credentialed study personnel specified on the MAY2015-05-01 Site Delegation of Tasks Logs. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

Forms required for study agent ordering, accountability, and return are available on the CPN website: http://cancerpreventionnetwork.org

6.6 Packaging and Labeling

Meriva® will be provided to MRIGlobal by Thorne Research, Inc. MRIGlobal is under contract with NCI, Division of Cancer Prevention to serve as the DCP Drug Repository.

Each bottle will be labeled with a one-part label identifying study specific information, including study title, DCP protocol number, investigator name, dosing instructions, number of refills, recommended storage conditions, the name and address of the distributor, Participant ID number, lot number, date of manufacture, final retest date, number of strength of tablets, and a caution statement indicating that the agent is limited to investigational use only and the agent should be kept out of reach of children.

6.7 Storage

In each institutional research pharmacy, capsules must be stored in a locked and secure area at room temperature, 59°-86° F (15°-30° C) and protect from light and moisture. Participants will be instructed to store their study agent in a location not accessible by children, at room temperature, and protected from light and moisture.

6.8 Pre-Registration and Registration/Randomization

6.8.1 Participant Pre-Registration

6.8.1.1 To pre-register a participant, the participating site will send the completed, signed, and dated Pre-Registration Eligibility Checklist, to the CPN Registration Office (Email: random01@mayo.edu; Fax: 507-284-0885) to pre-register all participants. The CPN Registration Office will enter the information into the CPN-hosted database. A unique participant identification number (PID) will be assigned.

6.8.1.2 At the time of pre-registration, the following will be verified:

- IRB approval at the registering institution
- Participant eligibility (including existence of a signed informed consent document)
- Existence of a signed authorization for use and disclosure of protected health information (USA Institutions only).
- Study agent is available and Drug Shipment Authorization has been granted to the registering site.

The following will also be recorded:

- Participant has/has not given permission to contact them or their physician to learn about the results from this study.
- Participant has/has not given permission for samples and related information to be sent from the Biobank to investigators at other institutions for use in future health research.
- Participant has/has not given permission to have three additional blood draws done along with protocol blood draws and that they may be used for future research to learn about, prevent, treat, or cure cancer and other health problems.
- Participant has/has not given permission to use information from the alcohol and tobacco use questionnaires to be used in future health research.
- Participant has/has not given permission to his/her doctor (or someone from the Cancer

Prevention Network) to contact them in the future to ask them to take part in more research.

6.8.1.3 Baseline (screening) evaluations must be completed within the guidelines specified on the Schedule of Events (See Section 7.1).

6.8.1.4 Registration Office personnel will automatically register participants separately to the translational components of the study (See Section 13).

6.8.2 Registration

6.8.2.1 To register a participant, the participating site will send the completed Registration Eligibility Checklist to the CPN Registration Office (Email: random01@mayo.edu; Fax: 507-284-0885). The CPN Registration Office will enter the information into the CPN-hosted database. For randomization details, see Section 13.2.

6.8.2.2 Intervention cannot begin prior to registration and must begin ≤ 14 days from registration.

6.8.2.3 Pathology reports confirming diagnoses will be placed in the study participant's file ≤ 30 days post Registration/Randomization.

6.8.2.4 Once the intervention assignment has been ascertained by the CPN Registration Office, the participant's study medication code numbers will be displayed on the emailed confirmation page. At least two weeks prior to the Month 3 visit, the data manager/nurse/pharmacist at the participant's institution must contact the CPN Registration Office at (507) 284-4130 for code numbers when additional study product is needed for the participant.

6.8.2.5 Stratification Factors collected at baseline (prior to randomization):

- Enrolling Site: Honduras versus Puerto Rico
- Gastric mucosal histologic diagnosis: MAG versus GIM versus Both (from screening EGD)

After the participant has been registered on to the study, values of the stratification factors will be recorded. Randomization will be performed by CPN personnel. The CPN electronic-based randomization system will be utilized to ensure that randomization of participants to appropriate study arms while balancing the stratification variables is carried out successfully.

6.9 Blinding and Unblinding Methods

Once the intervention assignment has been ascertained by the CPN Registration Office, the appropriate code numbers for the blinded study agent (Meriva® or placebo) will be communicated to the designated contact (i.e., data manager, study coordinator, nurse, or

pharmacist) at the participant's Participating Organization. This ensures that both the participant and the medical professionals who care for the participant are blinded to the intervention assignments.

There are two distinct situations in which it will be deemed appropriate to break the randomization assignment for participants enrolled onto this current trial:

- In the event of an emergency for an individual participant.
- Serious Adverse Event (SAE) that fulfills the criteria for expedited reporting to the FDA.

In these situations, Participating Organization personnel may assume the participant is on active agent and call the CPN Registration Office within one business day to receive unblinding information. The study name/number, participant identifier, participant initials, and bottle number will be required to break the randomization code. The Participating Organizations are responsible for notifying the medical monitor at DCP, NCI of the unblinding event. See Medical Monitor contact information in Section 11.2.

6.10 Agent Destruction/Disposal

At the completion of investigation and after receiving approval to do so from the CPN Compliance Coordinator, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Pre-Registration[1]	Screening/ Baseline[1]	Registration/ Randomization	Weekly (+/- 2 days)	Month 3 (+/- 7 days)	Month 6 or Early Termination (+/- 14 days)	Follow-Up – Month 7 (+/- 14 days)[2]
Informed Consent	X						
Assess Eligibility		X					
Medical History		X					
Physical Exam		X				X	
Alcohol and tobacco use assessment[6]		X				X	
Vital Signs (Ht, Wt, temp, pulse, BP)		X			X	X	
Laboratory Tests[3]		X			X	X	
Stool antigen testing for *H. pylori*		X					
EGD with biopsies		X[4]				X	
Research blood collection		X			X	X	
Pregnancy test, if applicable[5]		X	X				
Concomitant Medications		X		X	X	X	X

Evaluation/ Procedure	Pre-Registration[1]	Screening/ Baseline[1]	Registration/ Randomization	Weekly (+/- 2 days)	Month 3 (+/- 7 days)	Month 6 or Early Termination (+/- 14 days)	Follow-Up – Month 7 (+/- 14 days)[2]
Dispense Study Agent and Medication Diaries			X		X		
Collect/Review Study Agent and Medication Diaries					X	X	
Was It Worth It (WIWI)[6]						X	
Adverse Events				X	X	X	X
Telephone Contact				X			X

1. Pre-Registration and screening must take place ≤ 28 days prior to registration/randomization.
2. In the case of early termination, the follow-up phone call will take place 30 days (+/- 14 days) after the completion of the post-intervention visit tests and procedures.
3. Laboratory testing includes AST, ALT, Alkaline phosphatase, CBC (Platelets, Hemoglobin, WBC), BUN, Total bilirubin, Creatinine.
4. Eligibility will be determined based upon local pathology review. Pathology report documenting eligibility will be placed in the participant's study file. Specimens or images will be sent for central pathology review at the University of Puerto Rico. Discrepancies will be reviewed and resolved by both pathologists on a case-by-case basis.
5. A negative serum or urine pregnancy test (Individuals of childbearing potential only) must be documented ≤ 7 days prior to registration/randomization. If screening pregnancy test took place ≤ 7 days prior to registration/randomization, it does not have to be repeated.
6. Study participants may choose not to answer some or all of the questions on the assessments and questionnaire.

7.2 Baseline Testing/Prestudy Evaluation

7.2.1 Prescreening and Informed Consent

Participants will be identified by review of medical records and/or through implementation of the site recruitment plans. Potentially eligible participants will review the study events and risks in detail with site study team member and, if willing, sign the informed consent document. Participants will then be pre-registered and assigned a unique participant identification number.

7.2.2 Screening and Baseline

Initial screening will include a review of medical/surgical history, review of baseline symptoms, assessment of vital signs, physical examination, review of concomitant medications, and baseline alcohol and tobacco use assessment. If still eligible, blood will be drawn for clinical laboratory tests (AST, ALT, Alkaline phosphatase, CBC [Platelets, Hemoglobin, WBC], BUN, Total bilirubin, Creatinine) and for research. A stool antigen test will be performed to assess *H. pylori* infection. The participant will then undergo an EGD with biopsies (surveillance and research). Three sites (antrum, corpus, and incisura) will be biopsied (See Appendix D). Histologically-confirmed MAG, GIM, or both (at a minimum of one site) are required for eligibility and will be determined by the local pathologist. Specimen images will also be collected for central analysis. However, the results of the central review are not required prior to registration/randomization. Any discrepancies between the local and central pathologists will be resolved on a case-by-case basis by the two pathologists.

Screening/baseline activities must be completed ≤ 28 days prior to Registration/Randomization.

7.2.3 Registration/Randomization

Upon confirmation of eligibility, participants will be registered to the study and randomized to one of the two treatment arms. Participants will be dispensed a supply of study agent or placebo (200 capsules for 90 days), along with a medication/symptom diary and instructions for completion. Initiation of study agent (or placebo) must begin ≤ 14 days following registration/randomization.

7.3 Evaluation During Study Intervention

Participants will be contacted by telephone weekly (+/- 2 days) to assess compliance. Adverse events and concomitant medications will also be assessed and recorded.

At least two weeks prior to the Month 3 visit, the data manager/nurse/pharmacist at the participant's institution must contact the CPN Registration Office at (507) 284-4130 for code numbers to order additional study product for dispensing to the participant at the Month 3 visit.

At Month 3 (+/- 7 days), participants will return for a study visit, which will include an assessment of vital signs, safety and toxicity blood tests, adverse event and concomitant medications assessment. The study medication diary will be reviewed and collected. Any remaining study agent will be collected. A new study agent supply and medications diaries will be provided.

7.4 Evaluation at Completion of Study Intervention

The post-intervention evaluation will take place at Month 6 (+/- 14 days), or in the event of early termination. This evaluation will include assessment of adverse events and concomitant medications, follow-up alcohol and tobacco use assessment, WIWI questionnaire, a physical exam and assessment of vital signs, repeat safety/toxicity blood tests, a research blood collection, and repeat EGD with biopsies. Any individuals who discontinue intervention early for any reason will be encouraged to undergo the remaining tests and procedures as scheduled.

7.5 Post-intervention Follow-up Period

A follow up telephone call will take place at Month 7 (+/- 14 days). In the case of early termination, this phone call will take place 30 days (+/- 14 days) after the post-intervention visit. Adverse events will be assessed. If AEs are reported, the concomitant medications will also be assessed. Serious adverse events will be followed to resolution. All events will be assessed and treated according to institutional standards of good clinical practice.

7.6 Methods for Clinical Procedures

Participants will undergo EGD, after being NPO (Nothing Per Os) for a minimum of 6 hours. Pre- and post-procedure monitoring, administration of any sedation, and standard-of-care surveillance and biopsy collection will follow institutional clinical practice guidelines.

At baseline, eligibility will be determined in part by the histological confirmation of MAG, GIM, or both on at least one of the biopsies of the corpus, antrum, and incisura. The local pathologist's report will be used to confirm eligibility. Central pathological confirmation will be performed by the laboratories at the University of Puerto Rico. Specimen image submission for central review is described in Section 10.2.3.

At baseline and Month 6, research endoscopic biopsies will be collected for endpoint analysis. This will include one pass of the forceps with two bites of tissue at each of three sites (antrum, corpus, and incisura) will be collected for endpoint analyses. Research specimen processing is described in Section 10.2.4.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

The primary endpoint of this randomized trial is to compare the absolute change in IL-1β cytokine levels (measured by Luminex assay) in the gastric mucosa from baseline to 6 months among participants randomly assigned to receive either Meriva® or placebo. Statistical considerations regarding sample size and study power are based on this primary study endpoint (Section 13.4).

8.2 Secondary and Exploratory Endpoints

Secondary and exploratory endpoints are defined in Section 13.5.

8.3 Off-Agent Criteria

Participants may stop taking the study agent due to: completion of the planned intervention period, development of an adverse event or serious adverse event, inadequate agent supply, noncompliance, use of concomitant medications, medical contraindication, refusal, ineligibility (see Section 8.4), major treatment violation (see Section 8.4) or alternative treatment. Participants will continue to be followed, if possible, for safety according to the intended schedule of events (see Section 7).

Participants discontinuing the planned intervention prematurely will be encouraged to complete the Post-Intervention Evaluation tests and procedures as appropriate (if participant does not refuse, is not lost to follow-up, or unless it is clinically contraindicated). See Section 8.4 for further details as to data submission for participants deemed Ineligible after starting treatment or classified as a Major Treatment Violation (i.e., protocol requirements regarding intervention during the first week post-randomization were severely violated).

8.4 Off-Study Criteria

Participants may go “Off-Study” for the following reasons: development of an adverse event or serious adverse event, death, lost to follow-up, participant withdrawal, physician decision, protocol violation, complete study, or other (with detailed comments provided). Reason(s) will be noted in the participant’s research records, with the primary reason clearly identified. The participant will be classified as (Off Study/Off Agent). Data submission and follow-up after participants are determined to be “Off-Study/Off-Agent” for specific situations is noted below:

A registered participant is deemed ineligible if the participant did not satisfy each and every eligibility criterion at the time of study entry, for example, identified based on an audit or through the case evaluation process.

- If participants received study intervention, on-study materials and all data up until the point of confirmation of ineligibility will be submitted.
- If participants did not receive study intervention, on-study materials must be submitted. No further data submission is necessary. No follow-up is required.

Major Treatment Violation: A registered participant is deemed as being in major treatment violation by the coordinating center, if the participant's very first treatment/intervention administration is so grossly administered in error, that the participant's data can no longer be used for the primary endpoint. These cases are typically rare.

- On-study material and all data up until the point of confirmation of a major violation must be submitted.

Cancel/Participant Withdrawal: A registered participant is deemed a cancel if he/she refuses the study or withdraws consent before any study intervention is given. On-study material must be submitted. The Off Study case report form must be submitted. No follow-up is required.

8.5 Study Termination

NCI, DCP, as the study sponsor, has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

Our primary outcome is to compare changes in gastric mucosal IL-1β cytokine levels (as quantified with Luminex assay technology) after a 6-month intervention period in participants randomly assigned to receive Meriva® vs placebo. Secondary laboratory and biomarker outcomes include the assessment of additional gastric mucosal cytokine/chemokine levels (IL-8, TNFα, and IP-10, quantified with Luminex assay), gastric mucosal DNA damage (assessed by flow cytometry), and correlations with proinflammatory cytokine genotypes. The choice of these endpoints is based upon emerging preliminary data and the Vanderbilt University group's extensive experience in the field, as described in further detail in the following sections.

Gastric mucosal cytokines (Luminex assay). We will focus on IL-1β as a primary endpoint for this phase 2 trial, based on its compelling implication in *H. pylori*-associated gastric cancer risk,[55-59] and novel data generated by our investigative team showing that Meriva® administration can lead to decreased IL-1β protein levels in murine gastric samples (See Figure 1, Section 2.3). In Figure 1D, a significant decrease in mucosal IL-1β levels in mouse models is noted, as measured by Luminex assay. Intriguingly, in ongoing studies with human gastric biopsy samples obtained from patients with *H. pylori*-associated gastritis and gastric cancer, the Wilson lab at Vanderbilt has observed an increase in IL-1β in gastric tumors compared to paired non-tumor specimens, using Luminex assay technology. In addition, IL-8, TNF-α, and IP-10 (CXCL10) were increased in

both *H. pylori* infection and gastric cancers, as compared to histologically normal control tissues. Examination of IL-8, TNF-α, and IP-10 (CXCL10) mucosal levels have therefore been included in the present trial as secondary biomarker outcomes.

We will use the 38-plex Luminex assay kit (HCYTOMAG-60K MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel). Importantly, the Department of Pathology and Laboratory Medicine at the University of Puerto Rico has extensive expertise in multi-analyte, Luminex-based cytokine profiling in gastrointestinal tissues, including studies evaluating *H. pylori*-induced gastric inflammation and ulcerative colitis.[60, 61]

The scoring methods for Histology Gastric Score will follow the established protocol previously applied and reported by Correa and colleagues.[62]

Proinflammatory cytokine genotypes (IL-1β, IL-8, and TNFα SNPs) may correlate with gastric adenocarcinoma risk in the setting of active or prior *H. pylori* infection.[63] In our population-based studies in Honduras, we have begun to characterize these risk genotypes in the general population.[59, 64] Whole blood DNA will be obtained at the baseline visit for the determination of the risk genotype status and to fully characterize the host, which is part of our standard protocol in Central America. These genotypes, or other future genotypes, may provide the opportunity for precision medicine in the future and will be included as secondary outcome analyses, for the purpose of augmenting limited existing data and generating new hypotheses worthy of application to future gastric cancer chemoprevention studies in this population.

9.2 Comparable Methods

All methodology is identical to that used in previous, published research.[61,48]

10. SPECIMEN MANAGEMENT

10.1 Laboratories

Clinical Laboratories:
University of Puerto Rico
Laboratorio Intensivo Cooperativo – University Hospital
P.O. Box 2116, San Juan PR 00922-2116

Quest Diagnostics
#210 Carr 865, Toa Baja, PR 00949-5710

Hospital de Occidente
Ministry of Health
Santa Rosa de Copan, Honduras

Biomarker Analyses:

Keila L. Rivera Román MD, FCAP, FASCP
University of Puerto Rico
Dept of Pathology and Laboratory Medicine
Lab B342, 343
University of Puerto Rico
Medical Sciences Campus
Email: keila.rivera11@upr.edu

Maria Marcos, MD
Professor of Medicine
Department of Pathology & Laboratory Medicine
University of Puerto Rico
Medical Sciences Campus
Phone: 787-758-2525 x 2385, 1331
Email: Maria.marcos@upr.edu

Sara M. Gorbea Gonzalez, MT, CHS
Department of Pathology and Laboratory Medicine
Medical Sciences Campus, UPR
General Supervisor
Laboratorio de Inmunología y Enfermedades Infecciosas
Departamento de Patología y Medicina de Laboratorio,
Universidad de Puerto Rico Recinto de Ciencias Médicas,
PO Box 365067
San Juan PR 00936-5067
Tel. 787-766-0728
Fax 787-754-0710
e-mail: sara.gorbea@upr.edu

Kit Production and Specimen Storage:
Biospecimens Accessioning and Processing (BAP) Freezer
ST SL-16, 150 Third Street Southwest, Rochester, MN 55902
Telephone: 507-538-0602; Email: Neumann.roxann@mayo.edu

10.2 Collection and Handling Procedures

Research blood kits for shipping blood and tissue for all research analyses will be provided by BAP Kit Building (Biospecimen Accessioning and Processing Core Facility). Detailed collection, handling, and shipping instructions will be included with each kit. Participating Sites may obtain research kits by faxing the BAP Kit Supply Order Form to the number provided (found in the Forms Packet). At least two weeks should be allowed to receive the shipping kits. Kits will be

sent via FedEx® Ground at no additional cost to the participating institutions. They will not be forwarded by FedEx® rush delivery service unless the participating institution provides their own FedEx® account number. CPN will not cover the cost for rush delivery of kits. Because charges are incurred for all outgoing kits, a small, but sufficient, supply of specimen collection kits should be ordered prior to participant entry.

All sections of the requisition form, specimen submission CRFs, and specimen collection labels must be completed and legible.

Specimens should be sent overnight via FedEx® on dry ice. All samples must be shipped to the address provided on the specimen shippers.

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

10.2.1 Clinical Blood Specimens
Blood specimens for safety and toxicity monitoring will be drawn at Baseline, Month 3, and Month 6/Post-intervention, and analyzed locally according to local institutional standard procedures. See Section 7.1 for the list of specific tests.

10.2.2 Research Blood Specimens
Blood specimens for endpoint analyses as well as optional blood specimens for future unspecified research will be drawn at Baseline, Month 3, and Month 6/Post-intervention. Blood specimens will be processed into serum, plasma, and buffy coat, and shipped to BAP overnight. See Section 10.1 for address. Detailed instructions for collecting, processing, labeling, and shipping the specimens can be found in the instructions provided in each blood specimen kit.

10.2.3 Tissue Specimen Collection and Submission for Central Pathology Review
Histological confirmation of MAG, GIM, or both for eligibility will be determined based on local pathology review of the specimens collected during the baseline EGD procedure (See Appendix D). Representative specimens (blocks and/or slides) will be submitted for central review and confirmation. Digital images of all specimens will be created for the review and archiving processes. Discrepancies between local and central pathologists will be resolved on a case-by-case basis by teleconference or video conference between the local and central pathologists. Central pathology review will be performed at one time, when the study is completed, and is not part of the baseline evaluation.

Telepathology will be used to accomplish the goals of the study, and will be used as a pathology training platform. All specimens (histology slides) are de-identified. All study slides will be scanned and digitally archived for central review, discussion and training.

10.2.4 Research Tissue Specimens

Research tissue specimens will be collected at Baseline and Month 6/Post-intervention during the EGD procedures.

Biopsy specimens will be obtained during the EGD procedures. See Appendix D for locations from which the specimens will be collected. Specimens noted in Appendix D in green will be formalin-fixed and paraffin-embedded. At baseline, appropriate specimens will be sent to the local pathologist for determination of eligibility, i.e., presence of GIM and/or MAG. Remaining specimens will be used to determine Histology Gastric Score.

Specimens noted in Appendix D in red will be placed directly in screw-topped cryovials tubes with no preservative or buffer. The tubes will be snap-frozen by immersion immediately in dry ice or liquid nitrogen. To maintain the cold chain, specimens will be placed in a -70°C (or colder) freezer until shipment to BAP. See Section 10.3 for address. Shipping containers will be filled with 2-days' supply of dry ice, and all efforts necessary to prevent thaw during the shipping process will be implemented.

Biospecimen Summary

Specimen	Timepoint(s)	Processing	Shipping
Blood specimen for safety/toxicity monitoring. Specimen to be determined by local lab SOPS.	Baseline, Month 3, Month 6	Process according to local lab SOPs	Not applicable
H. pylori serology: Collect one 10mL no additive red-topped tube	Baseline	Process into serum, aliquot, freeze at -20°C or colder until shipment	Ship to BAP freezer (Address in Section 10.4) on dry ice for accessioning and storage. Storage at BAP will be at -70°C or colder; Ship in batches upon request by the University of Puerto Rico.
Mandatory: Stool testing for *H. pylori* antigen. Note: If a positive result is obtained, participant can be treated and then re-screened when a negative result is obtained.	Baseline	Collect and processing according to instructions in the stool antigen kit.	Not applicable
Risk genotype status: Collect one 10 mL (or two 4mL) EDTA purple-topped tube. Process using Qiagen Puregene solution in a 3:1 ratio	Baseline	Process EDTA purple topped tube into plasma and buffy coat, Freeze aliquots at -70°C or colder until shipment	Ship to BAP freezer (Address in Section 10.4) on dry ice for accessioning and storage; Storage at BAP will be at -70°C or colder; Ship in batches upon request by the University of Puerto Rico.
Optional research blood: Collect (1) one 10mL no additive red-topped tube and (2) one 10mL EDTA purple-topped tube,	Baseline, Month 6	(1) Process red-topped tube into serum (2) Process EDTA purple topped tube into plasma and buffy coat Freeze aliquots at -70°C or colder until shipment	Ship to BAP freezer (Address in Section 10.4) on dry ice for accessioning and storage. Storage at BAP will be at -70°C or colder.

Gastric biopsies noted in red in Appendix D	Baseline, Month 6	Place specimens in individual cryotubes, snap freeze immediately. Maintain at -70° C or colder until shipment	Ship to BAP freezer (Address in Section 10.4) on dry ice for accessioning and storage; Storage at BAP will be at -70°C or colder; Ship in batches upon request by the University of Puerto Rico.
Gastric biopsies noted in green in Appendix D	Baseline, Month 6	Formalin-fixed and paraffin-embedded.	At baseline, submit for central pathology review (See Section 10.2.3). Baseline and Month 6 blocks or slides will be used to determine Gastric Histology Score.

10.3 Labeling and Shipping Instructions

The pre-addressed shipping labels will be provided with the specimen kits. Site teams are cautioned to make sure the correct specimen is sent to the correct location for analysis.

All specimens must be labeled completely and legibly with the study number, site number, participant ID, type of specimen, date and time of collection:

Example:
MAY2015-05-01
MN026
CPN00023
EGD tissue biopsy
mm/dd/2016, 14:30

All sections of the requisition form and specimen collection labels must be completed and legible.

All specimens (except biopsy specimens that are formalin-fixed and paraffin-embedded) should be sent over night (Monday through Friday) via FedEx® or World Courier on dry ice. Site staff will send an email with shipping tracking information to the Biospecimen Resource Manager so arrangements can be made to receive the specimens and place immediately in appropriate storage facilities. Exceptions for holidays will be communicated in advance to participating organizations. All samples must be shipped to the address provided on the specimen shippers and listed above (See Section 10.1).

Roxann Neumann, Biospecimens Resource Manager
E-mail: Neumann.roxann@mayo.edu; Phone: 507-538-0602

Formalin-fixed, paraffin-embedded tissue (blocks or slides) from baseline and Month 6 EGD procedures will be sent to the University of Puerto Rico for central confirmation of baseline pathology review and for baseline and Month 6 measurement of Histology Gastric Score.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI.

At study completion, remaining frozen biologic specimens will be labeled (study number, participant ID number, specimen type, specimen number, date of collection) batched, and shipped (overnight, M-Th only) for storage (until request is received to transfer to DCP Biospecimens Repository) to:

Biospecimens Accessioning and Processing (BAP) Freezer
ST SL-16
150 Third Street Southwest, Rochester, MN 55902

At study completion, all remaining paraffin blocks and slides will be labeled (study number, participant ID number, specimen type, specimen number, date of collection) batched, and shipped (overnight, M-Th only) for storage (until request is received to transfer to DCP Biospecimens Repository) to:

CPN PC Office (Study MAY2015-05-01)
RO_FF_03_24-CC/NW Clinic
200 First Street Southwest, Rochester, MN 55905

At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events (CTCAE v4) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the active CTCAE (v4). The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4 as stated below.

CTCAE v4 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc.*
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, or definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) define an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon

appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found on the CPN website and on the DCP website at this location: **http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.**

11.2.2.2 Contact the DCP Medical Monitor by email (preferred) or phone **within 24 hours** of knowledge of the event.

Luz Maria Rodriguez, MD, FACS
National Institutes of Health, National Cancer Institute, Division of Cancer Prevention
9609 Medical Center Drive, Room 5E228
Bethesda, MD 20892
Phone: 240-276-7039
Fax (with cover sheet, Attn: Dr. L. Rodriguez): 240-276-7848
Email: rodrigul@mail.nih.gov

Include the following information when contacting the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 The Lead Organization and all Participating Organizations will submit SAE reports **within 48 hours** of learning of the event via the current, approved SAE reporting process:

The following individuals/entities will be provided with the SAE information within the 48 hour time frame:

1. The DCP Medical Monitor at rodrigul@mail.nih.gov
2. DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com
3. The CPN Operations Office at cancerpreventionnetwork@mayo.edu

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the CIRB/IEC.

11.2.3 Follow-up of SAE

Participating organization (PO) staff will submit follow-up reports as soon as they are available via the current, approved SAE reporting process. SAEs will be followed and treated according to institutional standards of good clinical practice. SAEs that are at least possibly related to study intervention will be followed until resolution.

12. STUDY MONITORING

12.1 Data Management

The Mayo Clinic Cancer Center database will be the database of record for the protocol and subject to NCI and FDA audit. Minimum Data Sets will be submitted to DCP per contract requirements. Please see 2012 CPN Master Data Management Plan.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used to create the electronic CRF (e-CRF) screens for data entry into the Mayo Clinic Cancer Center database. Amended CRFs will be submitted to the DCP Protocol Information Office for review and approval.

12.3 Source Documents

A source document is any document, form, or record where *specific participants'* data are first recorded. FDA [21 CFR 312.62 (b)] requires that the investigator "...prepare and maintain accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational agent or employed as a control in the investigation." Among many other items, source documents include:

- Inpatient and outpatient medical records
- Progress notes
- Consults
- Nursing notes
- Pathology reports
- Endoscopy reports
- Medicine/radiation administration records
- Surgical reports
- Laboratory reports

- Admission forms
- Flow sheets and worksheets that are signed and dated
- Protocol or study road maps
- Appointment books
- Participant diaries/calendars
- Blood and tissue collection/submission requisition forms (signed and dated).
- Case Report Forms (signed and dated):
    - Symptoms: Pre-Intervention
    - Physical Exam
    - Specimen Submission: Blood
    - Specimen Submission: Tissue

12.4 Data and Safety Monitoring Plan

The CPN Master DSMP, applicable to all studies within the CPN Consortium, has been modified for the purposes of this study. The MAY2015-05-01 DSMP provides detailed information regarding data and safety monitoring for this study. The trial will be monitored closely for occurrence of adverse events by the study team and by the Mayo Clinic Cancer Center Data Safety Monitoring Board (DSMB). The DSMB (along with the study Medical Monitor) will be consulted regarding whether or not accrual should be suspended to allow for investigation in the occurrence of severe adverse events, particularly for those that are possibly, probably, or definitely related to the study agent.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug

Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent supplied by DCP, NCI, used in this protocol, is provided to the NCI under a Collaborative Agreement (CRADA, CTA) between Thorne Research, Inc. (hereinafter referred to as Collaborator) and the NCI Division of Cancer Prevention. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" contained within the terms of award, apply to the use of Agent in this study:

12.7.1 Agent may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a patient participating on the study or participant's family member requests a copy of this protocol, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from the DCP website.

12.7.2 For a clinical protocol where there is an Investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-party Data").

12.7.3 NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

12.7.4 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

12.7.5 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

12.7.6 Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

12.7.7 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators of Collaborator's wish to contact them.

12.7.8 Any manuscripts reporting the results of this clinical trial must be provided to DCP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days (or as specified in the CTA) from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator for courtesy review as soon as possible and preferably at least three days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to the Protocol Information Office at NCI_DCP_PIO@mail.nih.gov.

The Protocol Information Office will forward manuscripts to the DCP Project Officer for distribution to the Collaborator. No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

The primary endpoint of this randomized trial is to compare the absolute change in IL-1β cytokine levels in the gastric mucosa from baseline to 6 months among participants randomly assigned to receive either Meriva® or placebo. We will also assess many secondary and translational endpoints.

There are limited Quality of Life (QOL) data on participants who participate in chemoprevention trials, and we intend to create a databank of QOL information by administering the "Was It Worth It" (WIWI) questionnaire at trial completion across multiple trials. We will seek to evaluate participant perception of their experience in trial participation once we have a reasonable amount of information (large enough sample size). Since participants who participate in these chemoprevention trials are high risk but otherwise healthy, the WIWI tool would help answer simple questions about participants' assessment of whether or not participation in this trial was "worth it." This is an optional questionnaire, which participants may decline to complete.

13.2 Randomization/Stratification

Participants will be randomized in a 1:1 fashion to one of two arms (Meriva® vs. placebo), using a dynamic allocation procedure called the Pocock-Simon,[35] which balances the marginal distributions of the stratifications factors across the intervention groups and has been shown to be able to accommodate a large number of factors (10-20) without difficulty.[36] For this study we will use the following stratification factors (collected at baseline, prior to randomization): enrolling site (Honduras or Puerto Rico) and gastric mucosal histologic diagnosis (MAG, GIM, or both).

13.3 Accrual and Feasibility

Planned Accrual Estimates

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	1	0	0	**1**
White	1	0	5	16	**22**
More Than One Race	0	0	1	1	**2**
Total	**1**	**1**	**6**	**17**	**25**

Racial Categories	INTERNATIONAL PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		**Total**
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	1	**1**
White	1	0	5	16	**22**
More Than One Race	0	0	1	1	**2**
Total	**1**	**0**	**6**	**18**	**25**

The study design requires a total of 100 participants for screening evaluation with approximately 50 moving forward to randomization (25 total participants per arm) due to anticipated screen failures of up to 50% prior to randomization. We further expect up to 12% of participants to drop out or otherwise become non-evaluable by 6 months, leaving 22 evaluable subjects per arm for the primary endpoint evaluation. We expect to randomize an average of 2-4 participants per month for each of the two participating CPN sites (Puerto Rico and Honduras), for an overall average accrual rate of 5-6 participants per month.

Amendment 6 Update: Because of delays related to regulatory and customs approvals, activation at Honduras was delayed by 15 months, which resulted in slower than expected overall accrual. Recently, the Honduras site discovered a higher than expected incidence of *Helicobacter pylori* infection, an exclusion criterion. In order to continue their expected recruitment pace, they expanded their outreach to more rural areas where *H. pylori* infection is somewhat less prevalent. They have also begun contacting participants who were screen failures in one previous study and who have completed another previous study as a group of known potential participants with high rates of study compliance. They are also reviewing lists of *H. pylori*-treated participants for evidence of gastric metaplasia and possible eligibility. The current anticipated completion date (last participant contact for the primary endpoint) is the 4th quarter of 2020.

13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary endpoint of this randomized trial is to compare the absolute change in IL-1β cytokine levels (measured by Luminex assay) in the gastric mucosa from baseline to 6 months among participants randomly assigned to receive either Meriva® or placebo. Statistical considerations regarding sample size and study power are based on this primary study endpoint.

In total, approximately 100 individuals will be screened and 50 participants will be randomized to receive Meriva® (n=25) or placebo (n=25), in order to achieve complete trial data on 22 evaluable participants in each arm (44 evaluable total). This assumes a 10% over accrual buffer after randomization to account for participants who are deemed ineligible, cancel, or dropout for other reasons during the intervention period. We expect to randomize approximately 5-6 participants per month across both the Puerto Rico and Honduras recruiting sites.

The null hypothesis for this study is that the absolute change in the IL-1β values from baseline to 6 months is the same or increased for Meriva® vs. placebo. The alternative hypothesis is that *Meriva® intervention will lead to a significant decrease in IL-1β cytokine levels from baseline to 6 months, as compared to placebo.* The proposed sample size and power calculations are based on prior unpublished data, where IL-1β levels are expected to have a mean of approximately 14 pg/mg protein at baseline, with a standard deviation of about 7.5 pg/mg of protein. This prior mouse study showed a 2-fold decrease in IL-1β levels for curcumin-treated mice (from around 14 to 7 pg/mg protein, comparing the vehicle [equivalent to placebo] treated to curcumin-treated mice). Based on this prior data, we expect the Meriva®-treated participants to have a mean decrease of about 7 pg/mg of protein or more by 6 months after baseline, leading to a 6 month IL-1β mean of 7 pg/mg of protein in the Meriva®-treated participants (2-fold decrease). For the placebo group, we expect the mean IL-1β to either stay the same or decrease slightly from baseline to 6 months.

With 22 evaluable participants per arm, this study yields 88% power to detect a mean decrease of 7 pg/mg protein or more in IL-1β level in the Meriva® intervention arm compared to a mean decrease of 0.5 pg/mg protein in the placebo arm (from baseline to 6 months), with an overall 1-sided significance level of 0.05 (2 sample t-test, assuming the same standard deviation of 7.5 pg/mg protein in each arm). If the data are not normally distributed, we will use the Wilcoxon Rank-Sum test for the primary endpoint analysis.

13.5 Secondary Objectives, Endpoints, Analysis Plans

Secondary Endpoints (prioritized order):
In participants with precancerous gastric lesions, to determine the effect of Meriva® versus placebo on the following endpoints (comparing the change from baseline to 6 months):

- Comparison of all adverse events between Meriva® and placebo
- Comparison of changes in Histology Gastric Score (HGS) from baseline to 6 months for Meriva® versus placebo
- Additional gastric mucosal cytokine/chemokine levels (IL-8, TNFα, and IP-10 quantified by Luminex assay);
- Comparison of gastric mucosal DNA damage, as assessed by IHC, of the biomarkers 8-OHdG and H2AX;
- Associations between proinflammatory cytokine genotype status (IL-1β, IL-8, and TNFα SNPs; characterized at baseline) and the above outcomes; these will be considered exploratory analyses.

Secondary endpoint biomarker data will be assessed from gastric mucosal biopsy samples obtained during upper endoscopy. Changes in the concentrations (or categories) of these endpoints from baseline to 6 months will be explored within and between the intervention arms. Fisher's exact tests, Wilcoxon rank sum tests, and two-sample t-tests will be used to assess differences between groups. McNemar's tests, Wilcoxon signed rank tests, and paired sample t-tests will be used to assess differences within each arm. Graphical methods (i.e. boxplots, scatter plots, etc.) will also be used to describe the data. Data for these secondary biomarker endpoints will be considered hypothesis generating and/or exploratory in nature.

Proinflammatory cytokine genotype status (IL-1β, IL-8, and TNFα SNPs) will be examined in relation to the outcomes above to further characterize the at-risk population and generate hypotheses for future studies.

13.6 Reporting and Exclusions

All randomized participants who are evaluated at baseline and 6 months and have IL-1β cytokine levels from those time points will be evaluable for the primary endpoint of this study using the modified intent-to-treat principle. We plan to over-randomize assuming 12% drop out within 6 months to ensure an adequate sample size in the primary analysis cohort. There will be

no imputation for missing data. A summary and listing of all major protocol violations will be provided. All details will be given in the final study report and/or manuscript. Participants lost to follow-up will be censored on the last date of assessment (or contact) and as appropriate for analyses that are dependent upon length of study participation.

13.7 Evaluation of Toxicity (secondary endpoint)

All participants will be evaluable for adverse events (AEs) from the time of their first dose of Meriva® or placebo. To evaluate the AE profiles associated with each arm, the maximum grade for each type of adverse event will be recorded for each participant and frequency tables will be reviewed to determine the overall patterns. The number and severity of adverse events (overall and by intervention group) will be tabulated and summarized. Grade 3+ adverse events will be similarly described and summarized separately. As per NCI CTCAE, toxicities are defined as adverse events that are classified as either possibly, probably, or definitely related to the interventional agent. Overall toxicity incidence, as well as toxicity profiles will be explored and summarized within and between the 2 intervention arms. Frequency distributions, graphical techniques, and other descriptive measures will form the basis of these analyses. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to the study intervention in the event of an actual association developing.

13.7.1 Adverse Event Stopping Rule

The trial will be monitored closely for occurrence of adverse events by the study team and by the Mayo Clinic Cancer Center Data Safety and Monitoring Board (DSMB) using the adverse event (AE) stopping rule specified below:

Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team in consultation with the Mayo DSMB may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Across all participants, accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria for each arm separately:

> If at any time 2 of the initial 10 treated participants or 20% of all participants (i.e. when accrual is greater than 10 participants) have experienced a grade 3 or higher adverse event.)

If at any time 1 participant experiences a Grade 4 or 5 AE that is at least possibly related to concomitant use of CYP sensitive substrate medications.

Each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. We will also review all grade 4 adverse events regardless of attribution to monitor the emergence of any previously unrecognized treatment related adverse event.

13.8 Evaluation of Response

All randomized participants who are evaluated at baseline and 6 months and have IL-1β cytokine levels from those timepoints will be evaluable for the primary endpoint of this study using the modified intent-to-treat principle. All conclusions regarding efficacy will be based on all participants who completed both baseline and 6 months and have IL-1β cytokine levels from those timepoints as well. Subanalyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of intervention, major protocol violations, etc.). However, sub-analyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported. For all measurements of response (i.e. the primary endpoint), the 95% confidence intervals will also be provided.

13.9 Interim Analysis

Not applicable

13.10 Ancillary Studies

Not applicable

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Good Clinical Practice" for all study personnel listed on the FDA Form 1572 and on the Delegation of Tasks forms for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Central Institution Review Board (CIRB) and Review of Ethics Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the University of Puerto Rico must obtain written approval to conduct the study from the appropriate CIRB. The Honduras site must obtain written approval to conduct the study from the appropriate Review of Ethics Board. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB/REB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the CIRB/REB, as applicable at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Place, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400; Fax: 650-691-4410

E-mail submissions: regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be forwarded electronically to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

No expenses will be incurred by the study participant and/or their insurance carrier. This does not include costs of tests and procedures that are a part of the participant's normal clinical care. This also does not include any injuries or illnesses the participant may have related to their participation on the study. In the event of an injury or illness, the study participant and/or their insurance carrier will be responsible for all expenses related to the injury or illness. Participants may be provided remuneration for their participation in the study, at the discretion of the local Institutional Review Board.

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Summary of Changes – Informed Consent Form

NCI Protocol #: MAY2015-05-01
Local Protocol #: MAY2015-05-01
Protocol Version Date: May 13, 2019

Protocol Title: Randomized, Double-blind, Placebo-controlled Trial of Meriva™ (curcuminoids) as a Candidate Chemoprevention Agent for Gastric Carcinogenesis

Informed Consent Version Date: May 13, 2019

Please note that the page numbers in the table below refer to the Word version of the Informed Consent Form that will be submitted to the CIRB.

#	Section	Page(s)	Change
1.	**Why is this study being done?**	2	The number of participants was revised for consistency with the revised schema.
2.	**What Extra Tests and Procedures....**	4	A typographical error was corrected.

NCI, DCP Consent Form Template for Consortia Cancer Chemoprevention Trials

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Consent Form

Study Title for Study Participants: Testing Meriva® to see if it has an effect on the development of stomach cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: MAY2015-05-01 Randomized, double-blind, placebo-controlled trial of Meriva ® (curcuminoids) as a candidate chemoprevention agent for gastric carcinogenesis

Introduction

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the research. Please take your time to make your decision about volunteering. You may discuss your decision with your friends and family. You can also discuss this study with your health care team. If you have any questions, you can ask your study doctor for more of an explanation. You should only agree to participate in this study when you are comfortable enough with the information so that you can make an informed decision about joining.

What is the usual approach to the changes in the tissues of my stomach?

You are being asked to take part in this study because you are at an increased risk for stomach cancer. Most people with multifocal atrophic gastritis (MAG) and/or gastric intestinal metaplasia (GIM) are watched by their doctors for worsening of symptoms, possible bacterial infections, and the possible development of stomach cancer.

What are my other choices if I do not take part in this study?

Taking part in this study is your choice. If you decide not to take part in this study, you have other choices, such as:

- You may choose the usual approach, which is to have your doctor watch for changes in your condition as described above,
- You may choose to take part in a different study, if one is available,
- Or, you may choose to do nothing.

Why is this study being done?

The purpose of this study is to compare the safety and effects of Meriva® with placebo and to see if the active agent can reduce the risk of stomach cancer by modifying any chronic inflammation or precancerous lesions found in the lining of the stomach. The U.S. Food and Drug Administration (FDA) considers Meriva® to be a botanical drug. It is not approved for the prevention of stomach cancer. Therefore, it is considered "investigational."

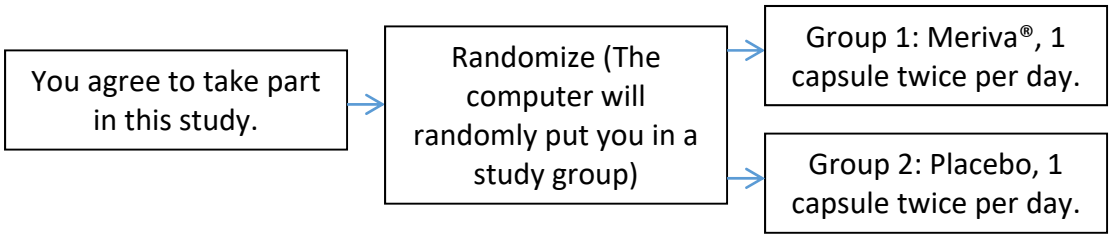
In this study, you will get either Meriva® or placebo. A placebo is a capsule that looks like the study drug but contains no active ingredients. The primary ingredient in Meriva® is curcumin, which is one of the substances that makes up the spice, turmeric. Turmeric is the main spice in curry.

About 100 people will take part in this study in Puerto Rico and Honduras.

What are the study groups?

This study has two groups. Group 1 will receive the study drug, Meriva®, and Group 2 will receive a placebo.

A computer will randomly put you in a study group—like a coin toss—to decide what group you get placed into. This is done because no one knows if one study group is better, the same, or worse than the other group. Once you are put in a group, you cannot switch to the other group. Neither you nor your doctor will know if you are receiving the study drug or placebo. Your doctor cannot choose which group you will be in.



How long will I be in this study?

You will be in the study for about 7 months. You will receive the study drug for 6 months. About one month after your Month 6 visit, a final phone call will be done to see how you are doing. Even if you do not finish the study, your doctor will continue to watch you for side effects and follow your condition for 7 months.

What extra tests and procedures will I have if I take part in this study?

Some of the exams, tests, and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study, we will review and sign this consent form together. You will then need to have the following tests and procedures to find out if you can be in the study:

- Physical exam and review of any symptoms you are experiencing
- Review of your medical and surgical history
- Review of the medications you are taking
- Assessment of your use of alcohol and tobacco,
- A stool test for a bacterial infection, *H. pylori*
- Blood tests for safety
- Blood tests for research
- Pregnancy test, if you are a woman capable of becoming pregnant.

If the exams, tests, and procedures show that you can take part in the study, and you choose to, you will undergo esophagogastroduodenoscopy (EGD), which is a procedure using a small scope to look at the lining of your esophagus (the swallowing tube that moves food from your mouth to your stomach), stomach, and small intestine (small bowel). During the EGD, biopsies of the lining of your stomach will be collected. These are small pieces of tissue from your stomach that will be examined under a microscope to see if there are any changes that might indicate an increased risk for stomach cancer.

As part of this study you will also be asked to answer questions about your tobacco and alcohol use, both before you begin the study and again at the Month 6 visit. Researchers want to see if tobacco and alcohol use affects the side effects people might get while on this study, or if tobacco and alcohol use modifies the effects of the study agents. These assessments will require about 10 minutes of your time.

During the study, you will take the Meriva® or placebo twice a day for 6 months. You should take the Meriva or placebo <u>with food</u> at about the same times each day, with the morning and evening meals, for example. Be careful to store the Meriva or placebo in a location that is out of the reach of children.

While you are on the study, the study team will call you every week to see how you are doing and discuss any medications you are taking and symptoms you might be having. You will be asked to keep a diary of your symptoms and the study drug that you are taking.

Half way through the study, Month 3, you will return for a brief checkup and blood tests for safety and for research. You will bring back any leftover medication you have and receive a new supply.

At about Month 6, you will return for a final visit. You'll have a physical exam, blood tests for safety and for research, a review of any symptoms you are experiencing and medications you are taking, follow-up assessment of your alcohol and tobacco use, and a final EGD with collection of biopsies. You will also be asked to fill out a short questionnaire about your experience in this study.

At about Month 7, you will receive a follow up phone call to see how you are doing and check on any symptoms you might still be experiencing.

The study calendar at the end of this document shows how often these tests and procedures will be done.

Please circle your answer to show whether or not you or your physician would like to be contacted to learn about the results from this study. You may participate in this study whether you respond "Yes" or "No."

YES NO

What possible risks can I expect from taking part in this study?

If you choose to take part in the study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss, for example about your tobacco and alcohol use
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or blood relatives could be found during a study.

Risks of the blood draw: You may have pain, bruising, a blood clot, or rarely, an infection at the site of the needle stick. You may be asked to avoid donating blood during and for one month after you stop taking a study drug.

Risks of the EGD with biopsies: There is a very small risk that the scope may cause a hole in the wall of your throat or stomach. If that were to happen, the doctor will arrange for surgery to repair it. There is a very small risk of bleeding related to the biopsy. These possibilities are considered rare but serious.

There is a small risk that you will have a reaction to the drugs that are given to make you more comfortable during the EGD procedure. You may have slowed breathing, a slowed heart rate, or you may feel sick to your stomach as the drugs wear off.

You will be given sedatives during the procedure. The sedatives may cause the following symptoms:

Likely:

- Increased sweating
- Low blood pressure

Less likely:

- Heartburn
- Rash
- Headache

Rare, but possibly serious:

- A muscle contraction (spasm) of the vocal cords that may briefly make it difficult to speak or breathe.
- Elevation in alkaline phosphatase and serum lactate dehydrogenase

If the first EGD (which you will have prior to taking study medication) is not part of your routine care (not a clinically scheduled routine biopsy), it is an added risk that you would have. The second EGD (which you will have after 6 months of taking study medication) is not part of your routine care and is an added risk related to participation in the study.

You should not drive, sign legal documents, or other similar activities for 24 hours after the procedure. You will need to arrange for someone to drive you home after the EGD procedures.

There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The table below shows the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Meriva®

Rare, Some May Be Serious In 100 people receiving Meriva, 3 or fewer may have:
• Loose stool (diarrhea) • Stomach ache • Feeling sick to your stomach (nausea) • Muscle pain (myalgia) • Joint pain (arthralgia) • Skin discomfort

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The study medication could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

This study may or may not help you because we do not know how the study drugs will compare to the usual approach for your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason by the sponsor, IRB, or FDA.

For the tobacco and alcohol use questions, you can decide to not answer some or all of the questions. Your decision will not affect whether you can participate in the study, and it will not affect your relationship with your doctor or the study staff.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call _____*<insert name of institution>* Institutional Review Board at _____*<insert telephone number>*.

What are the costs of taking part in this study?

The Meriva® or placebo will be supplied at no charge. The cost of study-specific biopsies and exams, tests, and any other procedures will be paid for by the study during the screening process and as long as you remain on the study.

The study will pay for the following:

- Meriva or placebo
- Physical exam, medical/surgical history review, recording of your vital signs
- Blood testing for safety and toxicity monitoring
- Pregnancy testing, if applicable
- Optional blood draws for research
- *H. pylori* stool antigen test
- EGD and biopsies, if completed at a time point different from your usual and routine clinical care
- Research biopsies, if the EGD is completed at a time point that is the same as your usual and routine clinical care
- All questionnaires and assessments

Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer.

You or your insurance company will pay for the following:

- EGD with biopsies, if the EGD is completed at a time point that is the same as your usual and routine clinical care

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

Will I be paid for participating in this study?

You will not be paid for participating in this study. However, you may receive a payment to help cover expenses related to study participation, such as travel.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us and we will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

- The study sponsor, NCI Division of Cancer Prevention
- Thorne Research, Inc., supplier of the Meriva®
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study
- The Food and Drug Administration and the National Cancer Institute in the US, and similar organizations if other countries are involved in the study

- **The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.**

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on **http://www.ClinicalTrials.gov**, as required by U.S. law. This Web site will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact _____*<insert study doctor(s) name(s)>* _____at *<insert telephone number.>*

<u>This section is about optional studies you can choose to take part in.</u>

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, and you or your study doctor will not know the results. You will not be billed for these optional studies.

You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples from your biopsies and blood. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about how genes affect health and disease, and these are called genomic studies. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in these optional studies, your blood and samples of your tissue will be collected. The researchers ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

- An additional blood draw that is separate from the main study will be performed and about 20 milliliters (4 teaspoons) of blood will be collected from a vein in your arm.
- Sample of your tissue will be collected during your EGDs. This is not extra tissue collected just for research. If there is any tissue left after the study analyses are complete, the remaining tissue will be used for future research.
- Your samples and some related information will be stored in the Biobank at the Mayo Clinic along with samples from other people who choose to take part.
- The samples will be kept stored at the Mayo Clinic until the end of the study, when they may be transferred to the National Cancer Institute.
- Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
- Neither you nor your doctor will be notified if/when research is conducted using your samples.
- Some of your genetic and health information may be placed in the central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

- The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
- There is a risk that someone could get access to the personal information in your medical records or other information we have stored about you.
- There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
- There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may not request your genetic information that we get from this research.
    - Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
    - Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.
    - Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance."

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

- When your sample is sent to the researchers, no information identifying you (such as your name or social security number) will be sent. Samples will be identified by a unique study code only.
- The list that links the unique code to your name will be kept separate from your sample and health information. Any Mayo Clinic Biobank and National Cancer Institute staff with access to the list must sign an agreement to keep your identity confidential.

- Researchers to whom the National Cancer Institute sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
- Information that identifies you will not be given to anyone, unless required by law.
- If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. Your samples may be helpful to research whether you do or do not have cancer. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part; however, you may receive some funds to defray some of the cost of participating (*e.g.*, parking, child care). If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the _____*<insert study doctor name>* at _____*<insert telephone number>* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact _____*<study doctor>* at _____*<insert telephone number>*.

Please circle your answer to show whether or not you would like to take part in each option:

SPECIMENS AND INFORMATION FOR FUTURE RESEARCH STUDIES:

My specimens from the three additional blood draws described in this consent form, along with related information, may be kept in a Biobank for use in future to learn about, prevent, treat, or cure cancer and other health problems.

YES NO

The information from my tobacco and alcohol use questionnaires may be used in future health research.

YES NO

My specimens and related information may be given to researchers at outside institutions

YES NO

I agree that my study doctors, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled "yes."

Participant's signature _____

Date of signature_____

Signature of person conducting the informed consent discussion _____

Date of signature_____

Optional Study Calendar

Time Point	Tests and procedures
Before you begin	• Review and sign the consent form
Screening and baseline	• Physical exam and vital signs (height, weight, blood pressure, heart rate, and temperature) • Review of your medical and surgical history • Review of symptoms you are experiencing and medications you are taking • Assessment of your use of alcohol and tobacco • Blood tests for safety and for research • Stool test for *H. pylori* infection • Pregnancy test, if appropriate • EGD with biopsies
Randomization	• Assigning you to one of the two study groups
Every day	• Take the study medication or placebo twice per day
Every week	• Phone call from the study team to see how you are doing
Month 3 (about Day 90)	• Study visit to collect unused study medication and receive a new supply • Brief check up • Blood tests for safety and for research • Review any symptoms you are experiencing and medications you are taking
Month 6 (about Day 180)	• Physical exam and vital signs (weight, blood pressure, heart rate, and temperature) • Review of symptoms you are experiencing and medications you are taking • Follow-up assessment of your use of alcohol and tobacco • Blood tests for safety and for research • Questionnaire (optional) about your experiences in this study • Repeat EGD with biopsies
Month 7 Follow up (about Day 210)	• Phone call from the study team to see how you are doing

APPENDIX A

Performance Status Criteria

Grade	ECOG Performance Status Scale Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B

Medication and Symptom Diary

Participant ID: ________________ **Physician:** ______________________ **Month**_______________**Year**__________

Instructions for you: This is a calendar for you to record how much medicine to take each day. If you develop any side effects from the medication, mark this on the calendar on the day you notice the effect. Use the back of this page to record any other symptoms you have or any other medications you take. Bring the bottles with any unused medication and your calendars with you when you return for your final visit.

Remember: Take your study medication at about the same times each day. **If you miss a dose, leave the check box blank for that dose.** If you have any questions, please contact: ____________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm
____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm
____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm
____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm
____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm	____ ☐ am ☐ pm

If you experience any other symptoms that you would like to report, please make note of them on this page. Be sure to write down the date the symptom appeared and the date the symptom disappeared. If you took any medications for the symptom or visited a doctor or hospital for the symptom, please inform the study team.

Participant signature _____, Date _____

Study Coordinator signature _____, Date _____

Appendix C. Was It Worth It (WIWI) Questionnaire

Visit type (Time point):* ☐ Month 6 (or early termination)

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study. Please respond to the following questions as indicated.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study? Y N U

If you had to do it over, would you participate in this research study again? Y N U

Would you recommend participating in this research study to others? Y N U

Directions: Circle one response

Overall, did your quality of life change by participating in this research study?

It improved It stayed the same It got worse

Overall, how was your experience of participating in this research study?

Better than I expected The same as I expected Worse than I expected

If there was <u>one thing</u> that could have been done to improve your experience in this research study, what would it be?

_____

_____

_____

Would you like to talk to someone about your concerns (circle one response)? Yes No

_____ _____

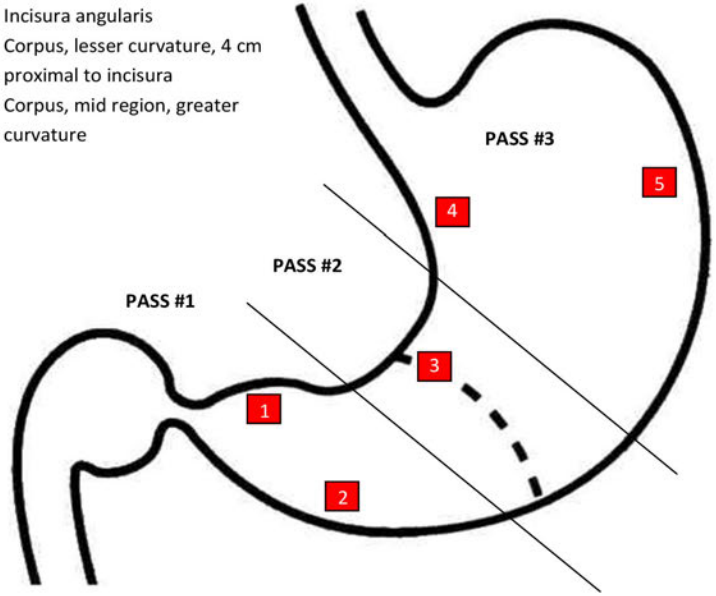
Signature Date

Appendix D. Gastric Biopsy Map

Study Biopsies—Snap Frozen

Biopsy Legend:

1. Antrum, lesser curvature, 3 cm from pylorus
2. Antrum, greater curvature, 3 cm from pylorus
3. Incisura angularis
4. Corpus, lesser curvature, 4 cm proximal to incisura
5. Corpus, mid region, greater curvature

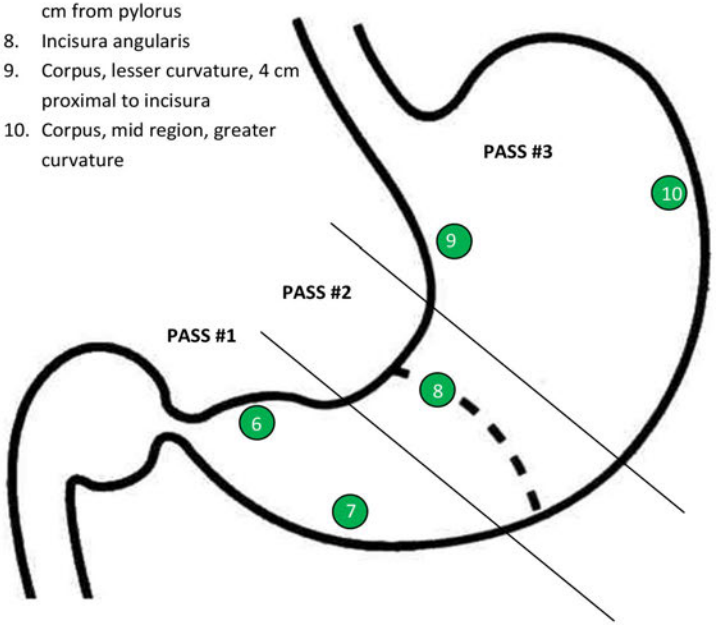


Biopsy Vial Legend:
Vial #1 = 1 and 2
Vial #2 = 3
Vial #3 = 4 and 5

Study Biopsies—FFPE

Biopsy Legend:

6. Antrum, lesser curvature, 3 cm from pylorus
7. Antrum, greater curvature, 3 cm from pylorus
8. Incisura angularis
9. Corpus, lesser curvature, 4 cm proximal to incisura
10. Corpus, mid region, greater curvature



Biopsy Vial Legend:
Vial #1 = 6 and 7
Vial #2 = 8
Vial #3 = 9 and 10
Baseline specimens will be sent for local pathology review for eligibility determination.

At least one bite in each biopsy point with the exception of the one in the Incisura Angularis (Points #3 and 8), which will have at least two bites.

Appendix E. Alcohol Assessment: Baseline

Instructions: For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of w or one and a half ounces of liquor.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage? *(check one)*
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Choose not to answer **(End)**
   - ☐ Don't know/Not sure

   (If No or Choose not to answer), stop assessment

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage? *(Enter the number of days drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)* _____
   (If more than 0, check one)
   - ☐ Week
   - ☐ Month
   - ☐ Year
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have day?
   *(Enter the average number of drinks per day)*_____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?
   *(Enter the number of days you had 5 or more drinks, or enter 0 if none.)*_____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost e day?
   (check one)
   - ☐ Yes
   - ☐ No
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularl
   (check one)
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Never drank regularly
   - ☐ Choose not to answer

Alcohol Assessment: Baseline (continued)

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average? *(Enter the number of drinks a day)*_____
   (If no answer, check one)
   ☐ Choose not to answer
   ☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly? _____ years
   (If no answer, check one)
   ☐ Choose not to answer
   ☐ Don't know/Not sure

9. At what age did you begin drinking regularly? _____ years of age
   (If no answer, check one)
   ☐ Choose not to answer
   ☐ Don't know/Not sure

10. What type(s) of alcohol do you drink?

Wine	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Liquor	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Beer	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Wine cooler	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer

Appendix E. Alcohol Assessment: Follow-Up

Instructions: For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. During the past 30 days, did you drink any alcoholic beverages? *(check one)*
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Choose not to answer **(End)**
   - ☐ Don't know/Not sure

   (If No or Choose not to answer, stop assessment)

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?
   (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.) _____
   (If more than 0), specify *(check one)*
   - ☐ Week
   - ☐ Month
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?
   (Enter the average number of drinks you had per day.) _____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day?
   _____ *(Enter the number of days you had 5 or more drinks, or enter "0" if none)*
   (If no answer, check one)
   - ☐ None
   - ☐ Choose not to answer
   - ☐ Do not know/Not sure

Appendix E. Tobacco Assessment: Baseline

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?
   - ☐ Yes
   - ☐ Choose not to answer → **Skip to Section B**
   - ☐ No → **Skip to Section B**
   - ☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette *(even one or two puffs)*? _____ Years old
   (If no answer, check one)
   ☐ Choose not to answer ☐ Don't know/Not sure

3. How old were you when you first began smoking cigarettes regularly? _____ Years old
   (If no answer, check one)
   ☐ Refused ☐ Don't know/Not sure ☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.
   (If you smoked less than one year, write "1.") _____ Years
   ☐ Choose not to answer ☐ Don't know/Not sure

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? *(A pack usually has 20 cigarettes in it).* _____ Number of cigarettes per day
   (If no answer, check one)
   ☐ Choose not to answer ☐ Don't know/Not sure

6. Do you NOW smoke cigarettes? *(check one)*
   - ☐ Everyday
   - ☐ Some days
   - ☐ Choose not to answer → **Skip to question 8**
   - ☐ Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette? *(check one)*
   ☐ Within 30 minutes ☐ After 30 minutes ☐ Choose not to answer

8. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*

   I smoked a cigarette today (at least one puff) *(check one)* ☐ Yes ☐ No
   1-7 days *(check one)* ☐ Yes ☐ No
   (If yes), Number of days since last cigarette _____
   Less than 1 month *(check one)* ☐ Yes ☐ No
   (If yes), Number of weeks since last cigarette _____
   Less than 1 year *(check one)* ☐ Yes ☐ No
   (If yes), Number of months since last cigarette _____
   More than 1 year *(check one)* ☐ Yes ☐ No
   (If yes), Number of years since last cigarette _____
   Don't know/Don't remember *(check one)* ☐ Yes ☐ No
   Choose not to answer ☐

Tobacco Assessment: Baseline (continued)

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes? *(check one)*
   ☐ Yes ☐ Choose not to answer
   ☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?
   Every day *(check one)* ☐Yes ☐No *(If yes)*, Number of times per day _____
   Some days *(check one)* ☐Yes ☐No *(If yes)*, Number of days _____
   (If yes), Per *(select one)* ☐ Week ☐ Month ☐Year

11. Which of the following products have you ever used regularly? *(Mark yes, no., or choose not to answer for all choices)*

Cigarettes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Traditional cigars, cigarillos or filtered cigars	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Hookah	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Bidis	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Snus	*(check one)* ☐Yes ☐No ☐ Choose not to answer
E-cigarettes or other electronic nicotine delivery system	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Pipes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Water pipe	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Clove cigarettes or kreteks	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Smokeless tobacco *(like dip, chew, or snuff)*	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Paan with tobacco, gutka, zarda, khaini	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Other, Otherspecify:	

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly? *(check one)*
   ☐ Within the past month (0 to 1 month ago)
   ☐ Between 1 and 3 months (1 to 3 months ago)
   ☐ Between 3 and 6 months (3 to 6 months ago)
   ☐ Between 6 and 12 months (6 to 12 months ago)
   ☐ Never used other forms of tobacco regularly
   ☐ Between 1 and 5 years (1 to 5 years ago)
   ☐ Between 5 and 15 years (5 to 15 years ago)
   ☐ More than 15 years ago
   ☐ Don't know/Not sure
   ☐ Choose not to answer

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker? *(check one)*
   ☐Yes ☐No ☐ Choose not to answer

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes ☐No ☐ Choose not to answer

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes ☐No ☐ Choose not to answer

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes → In total, for about how many years? _____ If less than 1, write "1."
   ☐No
   ☐ Choose not to answer

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes → In total, for about how many years? _____ If less than 1, write "1."
   ☐No
   ☐ Choose not to answer

Appendix E. Tobacco Assessment: Follow-Up

1. Do you NOW smoke cigarettes? *(check one)*
   - ☐ Everyday
   - ☐ Some days
   - ☐ Choose not to answer→ **Skip to Question 3.**
   - ☐ Not at all → **Skip to Question 3.**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? *(A pack usually has 20 cigarettes in it)*.
   _____ Number of cigarettes per day
   (If no answer, check one)
   ☐Choose not to answer ☐Don't know/Not sure

3. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*
   I smoked a cigarette today (at least one puff) *(check one)* ☐Yes ☐No
   1-7 days *(check one)* ☐Yes ☐No
   (If yes), Number of days since last cigarette _____
   Less than 1 month *(check one)* ☐Yes ☐No
   (If yes), Number of weeks since last cigarette _____
   Less than 1 year *(check one)* ☐Yes ☐No
   (If yes), Number of months since last cigarette _____
   More than 1 year *(check one)* ☐Yes ☐No
   (If yes), Number of years since last cigarette _____
   Don't know/Don't remember *(check one)* ☐Yes ☐No
   Choose not to answer ☐

4. Since your last visit, have you used other forms of tobacco, not including cigarettes? *(check one)*
   - ☐ Yes
   - ☐ Choose not to answer **(End)**
   - ☐ No (**End)** *(If no)*, stop assessment

5. How often do you/did you use other forms of tobacco?
   Every day *(check one)* ☐Yes ☐No *(If yes),* Number of times per day _____
   Some days *(check one)* ☐Yes ☐No *(If yes),* Number of days _____
   (If yes), per *(select one)* ☐Week ☐Month ☐Year
   ☐Choose not to answer

6. Since your last visit, which of the following products have you used? *(Mark yes or no for all choices)*

Cigarettes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Traditional cigars, cigarillos or filtered cigars	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Hookah	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Bidis	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Snus	*(check one)* ☐Yes ☐No ☐ Choose not to answer
E-cigarettes or other electronic nicotine delivery system	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Pipes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Water pipe	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Clove cigarettes or kreteks	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Smokeless tobacco *(like dip, chew, or snuff)*	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Paan with tobacco, gutka, zarda, khaini	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Other, Otherspecify:	

Tobacco Assessment: Follow-Up (continued)

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly? *(check one)*
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Choose not to answer
   - ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 -10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable

9. After the end of study treatment *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic *(check one)*
    - ☐ Smoked every day
    - ☐ Smoked some days
    - ☐ Did not smoke at all
    - ☐ Don't know/not sure
    - ☐ Choose not to answer
    - ☐ Not applicable (This is my first visit to this clinic)

Appendix F. Alcohol and Tobacco Cessation Resources

National and local resources to help with alcohol abuse and alcoholism

NIAAA's online guide ***Treatment for Alcohol Problems: Finding and Getting Help*** is written for individuals, and their family and friends, who are looking for options to address alcohol problems. It is intended as a resource to understand what treatment choices are available and what to consider when selecting among them.
https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm

Other resources:

National Institute on Alcohol Abuse and Alcoholism www.niaaa.nih.gov
301–443–3860

National Institute on Drug Abuse www.nida.nih.gov
301–443–1124

National Clearinghouse for Alcohol and Drug Information www.samhsa.gov
1–800–729–6686

Substance Abuse Treatment Facility Locator www.findtreatment.samhsa.gov
1–800–662–HELP

Alcoholics Anonymous (AA) www.aa.org
212–870–3400 or check your local phone directory under "Alcoholism"

Moderation Management www.moderation.org
212–871–0974

Secular Organizations for Sobriety www.sossobriety.org
323–666–4295

SMART Recovery www.smartrecovery.org
440–951–5357

Women for Sobriety www.womenforsobriety.org
215–536–8026

Al-Anon Family Groups www.al-anon.alateen.org
1–888–425–2666 for meetings

Adult Children of Alcoholics www.adultchildren.org
310–534–1815

National and local resources to help with quitting smoking

NCI's Smokefree.gov offers science-driven tools, information, and support that has helped smokers quit. You will find state and national resources, free materials, and quitting advice from NCI.

Smokefree.gov was established by the Tobacco Control Research Branch of NCI, a component of the National Institutes of Health, in collaboration with the Centers for Disease Control and Prevention and other organizations.

Publications available from the Smokefree.gov Web site include the following:

- Clearing the Air: Quit Smoking Today for smokers interested in quitting.
- Clear Horizons for smokers over age 50.
- Forever Free™ for smokers who have recently quit.
- Forever Free for Baby and Me™, in English and Spanish, for pregnant smokers who have recently quit.
- Pathways to Freedom: Winning the Fight Against Tobacco for African American smokers.

NCI's Smoking Quitline at **1–877–44U–QUIT (1–877–448–7848)** offers a wide range of services, including individualized counseling, printed information, referrals to other resources, and recorded messages. Smoking cessation counselors are available to answer smoking-related questions in English or Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m., Eastern Time. Smoking cessation counselors are also available through LiveHelp, an online instant messaging service. LiveHelp is available Monday through Friday, 8:00 a.m. to 11:00 p.m., Eastern Time.

Your state has a toll-free telephone quitline. Call **1–800–QUIT–NOW (1–800–784–8669)** to get one-on-one help with quitting, support and coping strategies, and referrals to resources and local cessation programs. The toll-free number routes callers to state-run quitlines, which provide free cessation assistance and resource information to all tobacco users in the United States. This initiative was created by the Department of Health and Human Services. For more information about quitlines, speak to an expert on the Smokefree.gov Web site.