Genotype-tailored Treatment of Symptomatic Acid-Reflux in Children with Uncontrolled Asthma

(GenARA)

Funding Agency:

Thrasher Research Fund

Phase III-IV Trial

Protocol Date:	**December 13, 2021**
Protocol Version:	**7.0**
IND Number:	**130170**
NCT ID:	**NCT03015610**
Principal Investigator (IND	**Jason E. Lang, MD, MPH** **Assoc Professor of Pediatric** [redacted] [redacted] **Duke University School of Medicine** [redacted] [redacted]

Statement of Compliance

This trial will be conducted in compliance with the protocol, International Council for Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the Canadian and United States Federal Regulations. The US regulations include but are not limited to 45 CFR 46 (Human Subjects Protection), 21 CFR 312 (Investigational New Drug), 21 CFR part 50 (Protection of Human Subjects, incorporating Subpart D Additional Safeguards for Children in Clinical Investigations, and 21 CFR part 56 (Institutional Review Board [IRB]) as well as international regulatory requirements, if applicable.

All individuals responsible for the design and/or conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the product label, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the effectiveness and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the Institutional Review Board (IRB) responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all participants with informed consent forms, as required by government and International Conference on Harmonisation regulations. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, part 312.64 and ICH GCP 4.11.

_____
Site Principal Investigator Name (Print)

_____ _____
Signature Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

The signature below documents the review and approval of this protocol and the attachments (e.g., package inserts), and provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

Jason E. Lang, MD, MPH

GENARA Study Principal

Investigator Name

Signature Date

Table of Contents

ASUI	Asthma Symptom utility index
AUC	Area under the curve
DAS	Duke Asthma Score
DSMB	data and safety monitoring board
EM	Extensive metabolizer
EPAC	Episodes of Poor Asthma Control
FEV1	Forced expiratory volume in 1 second
GERD	Gastroesophageal reflux disease
GSAS	GERD Symptom Assessment Questionnaire Score
HPLC	High Performance Liquid Chromatography
ICS	Inhaled corticosteroid medication
IM	Intermediate metabolizer
IRB	institutional review Board
LC/MS/MS	Liquid Chromatography/Mass Spectroscopy (2 Analyzers)
NAEPP	National Asthma Education and Prevention Program
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
NM	Normal metabolizer
NSAID	Nonsteroidal Anti-Inflammatory Drug
OFV	objective function value
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PM	Poor metabolizer
PMI	Precision Medicine Initiative
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
RTI	Respiratory Tract Infection
SABA	Short-Acting Beta Agonist
SF	Surgical gastric fundoplication
SNP	Single nucleotide polymorphism
UM	Ultra-rapid metabolizer
URI	Upper respiratory infection

PROTOCOL HISTORY OF CHANGES

Version	Date	Summary of Changes
1.0		N/A Original protocol
2.0		Removal of open label oral lansoprazole dose at V2 and PK blood draws Addition of Dr. Tarig Ali-Dinar to Key Personnel (Co-Investigator) (Key Roles section) Removal of references to Appendix throughout document Change of compensation to reflect less time-consuming and fewer invasive procedures (total compensation was $230 and now $120) Change of post-randomization in-person research visits to telehealth visits Replacement of daily diary cards with electronic diaries Addition of home spirometry
3.0		Addition of

Protocol Synopsis

Protocol Title: **Genotype-tailored Treatment of Symptomatic Acid-Reflux in Children with Uncontrolled Asthma (GenARA)**

Phase: III/IV

Product: Lansoprazole

Objectives: Primary: to determine if genotype-tailored PPI dosing significantly improves asthma symptoms in children with mild GERD and poorly controlled asthma.
Exploratory: to determine if genotype-tailored PPI dosing (a) significantly increases the risk for respiratory tract infection (RTI)

Study Design: Two center randomized, placebo-controlled, genotype-tailored, double masked efficacy study

Study Population:

Inclusion Criteria

- Age: 6-17-year-old with documented clinician-diagnosed asthma
- Evidence of recent uncontrolled asthma (must meet at least one of the following).
  - ACQ > 1.25
  - Use of short-acting beta-agonist for asthma symptoms twice/week or more on average over the past month
  - Nocturnal awakenings with asthma symptoms more than once per week on average over the last month
  - Two or more emergency department visits, unscheduled provider visits, prednisone courses or hospitalizations for asthma in the past 12 months
- Currently on daily inhaled corticosteroid medication (ICS) for asthma control equivalent to 88 mcg of fluticasone or greater for at least 6 weeks from the time of enrollment. Participant must be on NAEPP controller step 2, 3, 4 or 5 (5) (See Appendix B). Must be taking at on average >2days per week.
- Currently with mild GERD symptoms reported at V1 defined by a score on the Pediatric GERD Symptom Assessment Score greater than 15 and less than 80.
-
- Access to internet-connected device

Exclusion Criteria

- Taking daily *CYP2C19* substrates, inducers or inhibitors medication
- Past or current history of moderate-severe GERD or related disorders (erosive esophagitis, peptic ulcer disease, eosinophilic esophagitis) which in the opinion of the pediatric gastroenterology safety specialist/study physician requires treatment with acid-blocking agents.
- Daily use (i.e. 7 days/week) of a PPI for more than 4 consecutive weeks in the past 6 months;
- previous intubation for asthma,
- Previous surgery involving the esophagus or stomach (anti-reflux surgery, peptic ulcer surgery, trachea-esophageal fistula repair).
- Forced expiratory volume in 1 second (FEV1) < 60% of predicted at enrollment; Any major chronic illness that would interfere with participation in the intervention or completion of the study procedures.
  Current pregnancy, or recent pregnancy and currently lactating; females enrolled must agree to practice an adequate birth control method (abstinence, combination, barrier/spermicide, OCP) for the duration of the study.

- History of phenylketonuria (PKU).
- Medication use: treatment of GERD symptoms with over-the-counter antacids 4 days/week or more on average over past month.
- Theophylline preparations, azoles, anti-coagulants, insulin for Type 1 diabetes, digitalis, oral iron supplements when administered for iron deficiency within 1 month: Any investigational drugs within the past 30 days.
- Drug Allergies: previous allergic reaction from lansoprazole or other proton pump inhibitor medication or adverse reaction to aspartame.
- Inability to complete baseline measurements in a satisfactory manner according to the judgment of the research coordinator or site PI.
- Less than 70% completion of all fields in daily diary for asthma symptoms, SABA use and ICS medication adherence during the run-in period.
- Plan for family to move from study location within the next 6 months.

Number of Participants/ sites: 64 participants randomized / 2 sites

Duration of Participation : 26 weeks (2-week run-in +24-week intervention)

Outcomes: Primary: change in ACQ
Secondary: change in GSAS, ASUI; Annualized rate of exacerbation, EPAC, RTI

Dose Schedule:

Participants will then receive a single blinded daily dose (lansoprazole or placebo) by mouth daily for 24 weeks.

Daily Dosing (and volume)			
phenotype	%change*	<30kg	≥30kg
UM	100% ↑	30mg (10ml)	60mg (20ml)
EM	50% ↑	22.5mg (7.5ml)	45mg (15ml)
NM	0%	15mg (5ml)	30mg (10ml)
IM	30% ↓	10.5mg (3.5ml)	21mg (7ml)
PM	60% ↓	6mg (2ml)	12mg (4ml)
* - change from FDA recommended dose			

1. Key Roles

For questions regarding this protocol, contact:
Study Principal Investigator (IND Sponsor):

Jason E. Lang, MD, MPH
Division of Pediatric Pulmonary
and Sleep Medicine
Duke Health Center Creekstone
[redacted]

Study Co-Principal Investigator:

Tarig Ali-Dinar
Division of Pediatric Pulmonary and Sleep Medicine
[redacted]

Project Leader:

Joan Wilson RN
Research Program Leader
Department of Pediatrics, Duke University Medical Center
Divisions of Allergy/Immunology, and Pulmonary/Sleep Medicine
[redacted]

Jacksonville Clinical Site PI:

Kathryn Blake, Pharm.D., BCPS, FCCP
Director, Center for Pharmacogenomics and Translational Research
Principal Research Scientist
Nemours Children's Specialty Care
[redacted]

Sub-Investigators: Sub-investigators are included in the signature log and consent form(s) at each clinical site.

FDA Contact:

Laura Musse, RN, MS, CRNP
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
[redacted]

Sponsor Contact:

Brittni Smith, PhD

Thrasher Research Fund
[redacted]

2. Background Information & Scientific Rationale

2.1. Summary of Study Background Information

New approaches are needed to control asthma because breakthrough asthma symptoms continue to cause suffering, cost, and disability, particularly in high-risk groups such as children and patients with co-morbidities. Asthma now affects roughly 1 in 10 children (7). Despite the longstanding presence of published guidelines (5), asthma remains difficult to control in many patients particularly minority children (8) and children with co-morbid conditions such as obesity (9) and gastro-esophageal reflux disease symptoms (10). Year after year asthma is a leading cause of urgent care visits, ED visits, hospitalizations and ICU admissions (11). Asthma also causes chronic relapsing symptoms that do not always lead to healthcare utilization but causes chronic disability and diminished quality-of-life. Chronic mild symptoms can lead to frequent self-medication, reduced sleep quality, impaired concentration in school and reduced extracurricular participation. The presence of obesity and GERD are associated with more of these chronic symptoms and lower quality of life in asthmatic children (6). Personalized approaches tailored to at-risk, high morbidity groups hold promise for improving asthma care. Years of evidence suggest a link between GERD and asthma (12-19), and recently we have shown that GERD symptoms are closely associated with asthma symptoms in children. Decades of data resulting from animal models (20-23), epidemiologic studies (12, 17), human esophageal acid instillation studies (24-33), pH probe asthma symptom correspondence studies (34), surgical fundoplication follow-up studies (35-39), and anti-GERD drug studies (40-43) all strongly suggest a link exists between GERD and asthma. These findings support the mechanism of gastric refluxate moving into the esophagus and activating acid-sensitive esophageal nerve fibers which cause vagus nerve-mediated airway triggering, or cough which is attributed to asthma. Using a large longitudinal analysis, we found that children with baseline GERD are at an increased risk of developing subsequent physician-diagnosed asthma (figure 1). We recently discovered a direct association between increasing GERD symptoms and asthma symptoms scores in overweight and obese children (figure 2). Overweight and obese children had significantly worse asthma symptoms compared to similar leans (44). When we adjusted for GERD scores, the greater asthma symptoms reported in obese children were abolished suggesting that GERD may be mediating asthma (44).We also found that a second replicate cohort showed a significant association between GERD scores and asthma scores in both lean and obese asthmatic children (45). As much as 85% of asthmatic children experience clinically significant GERD (46), and we recently published that >95% of overweight/obese asthmatic children reported two or more different GERD-related symptoms just in the preceding 7 days (6). Overall, these data support the idea that PPI intervention would improve asthma control in children with symptomatic GERD. Past trials studying the effect of acid-blockers on asthma symptoms have shown promising but inconsistent results which we propose is the result of a predictable PPI pharmacogenetic effect. The current literature suggests that anti-GERD medications do not consistently improve asthma outcomes in a diverse cohort of patients with GERD symptoms. However, a close review of the literature shows that among the majority of controlled studies there is consistently some efficacy signal that is unlikely due to chance. What is

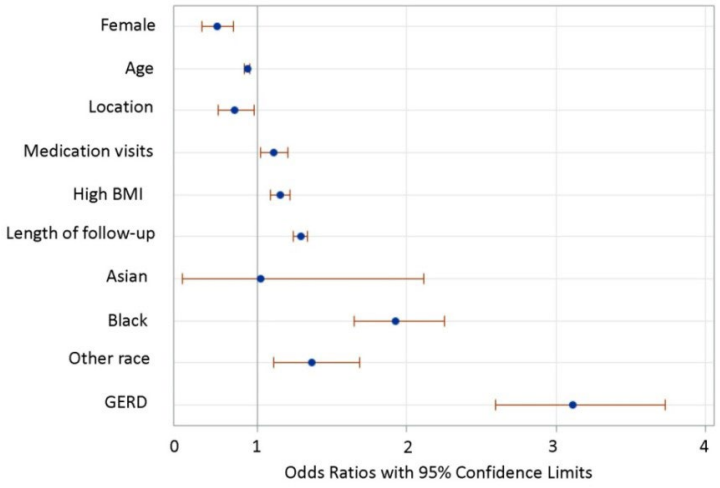


Figure 1: Risk Factors for Incident Asthma among 23,361 children with GERD and 23,360 matched controls without prior GERD in a retrospective longitudinal cohort design. Both groups were without current or prior asthma at baseline. Controls were matched one-to-one by age, race, location, gender and length of follow-up to reduce bias. All participants were taken from Nemours' four primary sites between January 1, 2008 and June 30, 2014. Incident asthma was defined as at least two diagnoses (ICD-9 493.x) AND a prescription of at least one anti-asthma controller medication. Using step-wise backward logistic regression, and adjusting for sex, race, ethnicity, observation period, and BMI, GERD was the strongest risk factor for incident asthma (OR=3.2, p<.0001). Location refers to Delaware versus Florida patients. BMI = body mass index, GERD = gastroesophageal reflux disease.

more likely is that current conventional PPI dosing is effective only for particular PPI responder groups. Current FDA-approved "conventional" lansoprazole dosing in children recommends just two different doses for children up through adolescence based on weight (<15kg: 15mg once daily; ≥15kg: 30mg once daily). Two recent systematic reviews concluded that PPIs most likely help subsets of patients with asthma (12, 47). Our preliminary work suggests that "PPI responders" are those with the normal PPI metabolizer phenotype who do not require dosing adjustments. Fewer PPI studies have been conducted in asthmatic children, however there is some evidence for significant asthma improvements with anti-GERD therapy (40-42). Partial or inconsistent response from a drug that is known to have variable clearance within the population (as do PPIs) is suggestive of a pharmacogenetic effect.

2.2. Scientific Rationale

2.2.1. Relationship between GERD and Asthma

The relationship between symptomatic GERD and asthma has been long debated and remains unresolved. Cross sectional analyses (which show that one condition is more common in the other) do not contribute to the understanding of sequence and causality. However, as we have found in a recent large longitudinal cohort analysis in which all children were without asthma at baseline, antecedent GERD increases the risk for subsequent incident asthma (fig 1) compared to matched children without GERD. These findings from a large epidemiologic database are robust because the methodological approach addressed the traditional limitations of EHR database research, including adequate and compatible computer systems, inconsistent data standards across sites, lack of quality-control checks during data creation, collection and entry, and large-scale data cleaning. Though the mechanism for this epidemiologic association remains unclear, it is clear from these real-world longitudinal data involving >46,000 children, GERD does antedate and increase the risk for later asthma.

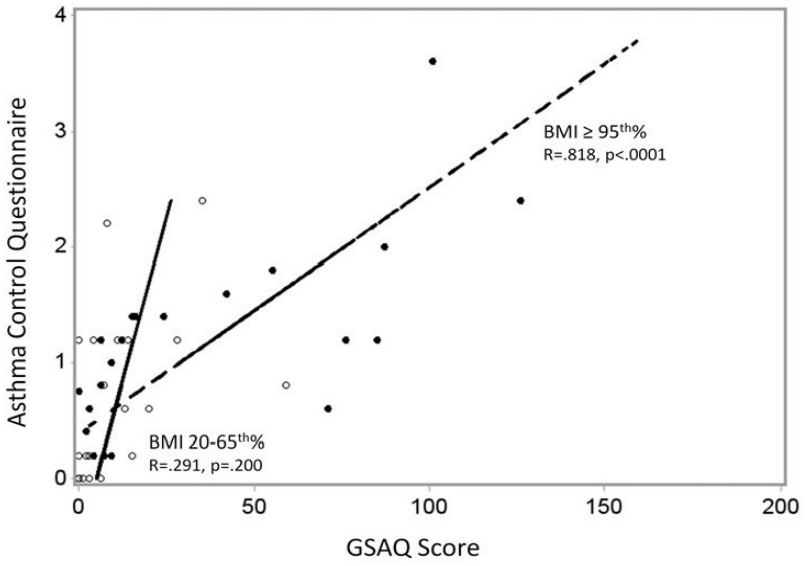


Fig 2. GER Symptoms are highly associated with Asthma Symptoms in Obese Children (R=.818, p<.0001). GSAQ – GERD Symptom Assessment Questionnaire Score, ACQ – Asthma Control Questionnaire.

The mechanism that leads from GERD to incident asthma is likely to also be a factor in worsening asthma symptoms among children with underlying asthma. We recently found that overweight/obese children (n=35) with rigorously confirmed asthma had frequent GERD symptoms (>95% prevalence) and that scoring of GERD symptoms using a validated pediatric symptom measure (the GSAS) closely associated with severity of asthma symptoms (figure 2). A replicate cohort involving 306 children and adolescents with asthma also demonstrated significant association between GERD symptoms and asthma symptoms in all children regardless of obesity status (Leans: R=.317, p=.001; Obese: R=.507, p<.0001). Interestingly, this replicate cohort of 306 children with asthma excluded children with diagnosed GERD at the time of enrollment. Among these children, the GSAS ranged from 0 to 276 with a mean (SD) = 18.6 (29.5). Thus, to include only 'mild' GERD, we will exclude children at enrollment with a GSAS>80. This threshold is chosen as it was 2 SD above the mean GSAS for a group of children and adolescents without reported GERD at baseline.

2.2.2. Pharmacokinetics and treatment efficacy of PPIs depend on the highly polymorphic *CYP2C19* gene

Despite documented variability in treatment response (48, 49), PPIs are generally viewed as the most efficacious group of acid-blocking agents because they overcome the redundant physiological control of acid secretion by inhibiting the gastric H+/K+ -ATPase, the final effector in the acid secretion pathway of gastric parietal cells. PPIs all act by covalently binding to the H+/K+-ATPase proton pump leading to reduced outflow of H+ ions into the canalicular space. Despite their short half-lives (1-4 hours), PPIs maintain their anti-secretory effect for 24-48 hours (50-52) (i.e., PPIs achieve a pharmacodynamic stead-state). PPIs are rapidly absorbed when taken orally, and clearances vary from 22-44% of liver blood flow in adults (53, 54) and children (55-58). Most PPIs have distribution volumes that are 8%-20% of total body water and are metabolized mainly by *CYP2C19*. The *CYP2C19* gene that encodes the *CYP2C19* hepatic enzyme is located on chromosome 10q24.1-q24.3, has 9 exons and is highly polymorphic (59-61). The metabolism and pharmacokinetics of PPIs vary greatly from person-to-person because the *CYP2C19* gene has both gain-of-function and loss-of-function alleles (2). The relatively common point mutation G681A (minor allele frequency: 10-30%) causes an aberrant splice site in exon 5 resulting in a premature stop codon and a non-functional protein, and is responsible for the *2 allele (the most prevalent loss-of-function allele) which has significantly reduced clearance compared to normal metabolizers (NM)(62). Several losses of function alleles (*n=loss-of-function allele, e.g., CYP2C19 SNPs: *2 rs4244285; *3 rs4986893; *8 rs41291556; *9 rs17884712) reduce drug clearance and significantly increase AUC resulting in individuals being classified as either poor or intermediate metabolizers (PM or IM). *CYP2C19**17 is a gain-of-function allele that has demonstrated increased transcriptional activity (63, 64) and appears to increase the clearance of PPIs. Depending on the *CYP2C19* diplotype, individuals can be classified as poor metabolizers (PM; 2 *n alleles), normal metabolizers (NM; 2 wildtype (*1) alleles), intermediate metabolizers (IM; *1/*n), extensive metabolizers (EM; *1/*17) or ultra-rapid metabolizers (UM; *17/*17 alleles) (table 1). The wild type (WT) *CYP2C19**1 alleles are associated with rapid clearance and are responsible for individuals being classified as normal metabolizers (NM)(60). Individuals carrying *1/*17 or *17/*17 alleles contribute to the extensive and ultrarapid metabolizer phenotypes (EM or UM), respectively (65, 66). Individuals carrying the *2/*17 diplotype have also been identified. The effect of *2/*17 diplotype on PPI AUC is not clear. AUC in carriers of *2/*17 was higher in some studies compared to WT (67, 68) and similar to

Table 1. Definition of *CYP2C19* Metabolizer Phenotype (1)

ALLELE[a]	GENOTYPE	ALLELE ACTIVITY	Metabolizer Phenotype	Frequency (2) (pan-ethnic cohort)
*1/*1	Wild Type (WT)	2 active alleles	Normal Metabolizer (NM)	41%
*1/*n	Heterozygous WT	1 active allele 1 inactive allele	Intermediate Metabolizer (IM)	21%
*2/*2 or *n/*n	Homozygous mutant	2 inactive alleles	Poor Metabolizer (PM)	3%
*1/*17	Heterozygous WT	1 active allele 1 increased activity allele	Extensive Metabolizer (EM)	24%
*17/*17	Homozygous mutant	2 increased activity alleles	Ultrarapid Metabolizer (UM)	4%
*2/*17	Heterozygous mutant	1 inactive allele 1 increased activity allele	?	6%

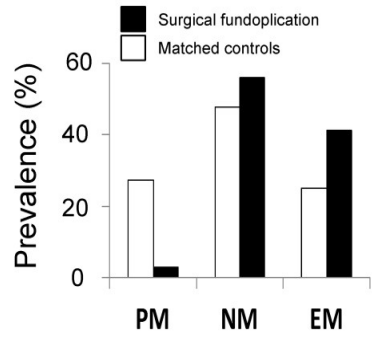
a - *2, *3, *8, or *9 refer to loss-of-function (inactive) alleles; n – refers to any of the loss-of-function alleles, IM and PM will be combined in this proposal as PM based upon recent data (3).

WT in another (66). Our preliminary data from a study of lansoprazole support AUCs being similar among WT and *2/*17 carriers (figure 3) and will be considered as NM for the current study. Overall, the AUC following the administration of equal PPI doses given to adult PMs and EMs can vary 3-10-fold (53, 54, 69-71). Importantly, little to no PK research among *CYP2C19* metabolizer phenotypes has been conducted in children.

2.2.3. Effect of *CYP2C19* genetic variation on responsiveness to PPI

Studies from both adults and children demonstrate that the efficacy of PPIs to treat GERD and related conditions are closely linked to plasma concentrations (58, 72-74). Numerous studies in adults have shown that *CYP2C19* variants markedly influence the PK and PD of PPI (53, 54, 59-61, 75-77). Patients needing acid-suppression who are extensive (EM) or ultra-rapid (UM) metabolizers have higher treatment failure rates compared to NMs when given conventional dosing (53, 54, 78). Additionally, *H. pylori* cure rates are significantly higher among PMs compared to EMs (69, 70) and higher doses of PPI are required to eradicate *H pylori* in EMs (70, 79). The same effect would be expected in children but has not been proven and thus pediatric PK studies are greatly needed. Some early reports suggested that *CYP2C19* did not affect PPI levels in children, however recent studies have now demonstrated the importance *CYP2C19* variants (66, 80, 81) on drug levels. For example, the clearance of pantoprazole was estimated in pediatric patients from birth to 16 years and was 70% lower in PMs compared to EMs (82). In a small number of patients, we recently found that metabolizer phenotype does affect PPI serum concentration in children (figure 3). Furthermore, our group has recently found a higher-than-expected prevalence of extensive and ultra-rapid metabolizer phenotypes (EM and UM) among a cohort of children failing PPI treatment and requiring surgical gastric fundoplication (SF) (figure 4). These data are consistent with EM+UM children needing genotype-tailored (increased) dosing of PPI to avoid treatment failures. Aim#2 of the current study will provide valuable data regarding the pharmacokinetics of PPIs in children stratified by *CYP2C19* genotype and metabolizer phenotype. This knowledge is significant because it is novel—we are not aware of any PK studies of PPIs in children which take into account genetic variation. Currently, the lansoprazole label describes possible drug-drug interactions with other drugs that are metabolized by *CYP2C19*, though current dosing recommendations do not utilize metabolizer phenotype to optimize dosing. Currently the PPI dosing for children is largely extrapolated from adult findings which for drugs used in children that are influenced by genetic variation is a major health and safety concern.

Figure 4. Comparison of CYP2C19 phenotype frequencies among children undergoing fundoplication surgery and matched controls. PM – poor metabolizer, NM – normal metabolizer, EM – extensive metabolizer.



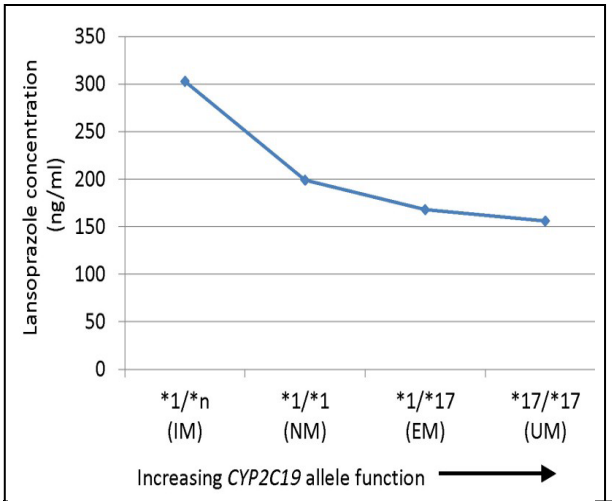


Figure 3: Diplotype of *CYP2C19* affects lansoprazole pharmacokinetics in children.

Phenotype	Alleles	Number (%) of Participants	Mean ±SD LZ Con. ng/ml
IM	*1/*2 or *3	13 (32%)	303±165
NM	*1/*1	11 (27%)	199±137
EM	*1/*17	11 (27%)	168±146
UM	*17/*17	2 (5%)	156±123
?	*2/*17	4 (10%)	201±57.1
p=0.131, ANOVA test for linear trend			

We compared drug levels following a single dose of conventionally dosed lansoprazole with CYP2C19 genotype/metabolizer phenotype in 41 children with GERD and found a direct relationship between *CYP2C19* diplotype and lansoprazole concentration (figure 3, p=.131, test for trend). Since serum PPI concentrations correlate with clinical response, diplotype is also very likely to be important in affecting both treatment success and risk of adverse events. Our group recently found that EM children (n=21) on conventional PPI dosing and undergoing esophageal pH probe testing had inadequate acid-blockade compared to NM+PM (n=53) (% time pH<4: 5.7 vs. 2.7, <.01; acid clearance (seconds): 180.7 vs. 106.8, <.001). In addition, our group recently assessed all children who failed PPI therapy and subsequently underwent a surgical gastric fundoplication (SF) within our institution who also had available endoscopic tissue samples for DNA genotyping. We compared these children to race-matched controls also taking PPI but who did not require fundoplication? The children failing PPI therapy and requiring fundoplication were significantly more likely to have the EM metabolizer phenotype compared to controls (41% vs. 25%, p<.01) (figure 4). In addition, significantly fewer children failing PPI and needing fundoplication had the PM metabolizer phenotype compared to controls (3% vs. 27%, p<.01). Collectively, these data strongly support our hypothesis that EM and UM children will benefit from a genotype-tailored (higher) dose of PPI to achieve optimal anti-secretory response. These findings are relevant to the current proposal because it argues that EM and UM children with GERD and asthma are being under-dosed on conventional PPI dosing.

Table 2: Proton Pump Inhibitors and Pediatric Infections

ICD9	Acute Conditions	RR	χ2 pvalue
008.45_	Intestinal infection Clostridium difficile	6.55	1.48E-08
461.8_	Other acute sinusitis	2.64	2.51E-05
079.2_	Coxsackie virus infection	2.19	7.58E-03
486_	Pneumonia, organism unspecified	1.47	3.08E-08
461.9_	Acute sinusitis, unspecified	1.28	4.16E-09
382.9	Otitis media, unspecified	1.21	8.75E-06
ICD9	Chronic Conditions	RR	χ2 pvalue
491.1_	Mucopurulent chronic bronchitis	7.00	3.69E-10
473.2	Chronic ethmoidal sinusitis	5.25	2.28E-08
473.8_	Other chronic sinusitis	4.76	6.28E-24
558.3_	Allergic gastroenteritis and colitis	4.15	1.00E-22
473.9	Unspecified sinusitis (chronic)	2.13	1.40E-37
472.1_	Chronic pharyngitis	1.97	1.38E-03
473.0_	Chronic maxillary sinusitis	1.91	1.31E-07

2.2.4. Importance of CYP2C19 variation in PPI-related adverse side effects

In addition, treatment with PPI have consistently been associated with a number of adverse side-effects including C. difficile colitis (83-85) and respiratory infections (83, 86). We analyzed longitudinal data from 36392 asthmatic children from 2000-2015 in the Nemours multi-state bioinformatics database. Asthmatic children recently prescribed a PPI were matched using a 1:4 ratio with similar asthmatic children (matched by race, ethnicity, sex, age at diagnosis, total observation period, and insurance status) with no previous PPI prescription, resulting in 2291 PPI (positive) and 9164 PPI (negative) children. Risk of incident acute and chronic aerodigestive infections were significantly greater following PPI (table 2).

These data are consistent with PPI exposure increasing the risk for several acute and chronic respiratory and gastrointestinal infections which would be expected to worsen asthma symptoms. These data do not assess genotype. However, since IM and PM children make up roughly 25% of the population, a cohort this size would have the power to demonstrate an association between PPI and infections even if the effect was exclusive only to IM and PMs. In a study of 306 asthmatic children without significant GERD at baseline, we showed that PPI use at conventional doses for 6 months was associated with significantly greater sinusitis, strep throat and URI, using serial participant interviews (4). In a subsequent genetic sub-study, we showed that participants with one or more CYP2C19 loss-of-function alleles (IM or PM) had significantly higher serum lansoprazole levels compared to NM and were significantly more likely to suffer respiratory adverse events related to URI and strep/sore throat (3). Furthermore (and germane to this proposal), we showed that these same PM participants developed worse asthma control (triggered by URI) compared to NM after 4 months on conventional PPI

dosing (87). These data are important to the current proposal and to clinicians treating patients with GERD and asthma because conventional dosing of PPI in these IM and PM patients is likely to improve GERD symptoms at the cost of greater risk of URIs. Since URIs are the most common trigger for loss of asthma control in children, conventional dosing will ultimately not help asthma control. Instead, these children who have the IM or PM genotype could be given a genotype-tailored (lower) dose which will provide normal serum concentrations and improved GERD symptoms without the risk of excess URI. Aim#1 of our proposal employs a dosing adjustment based on pediatric PK principles from available data in children (1) to try to demonstrate that genotype-tailored PPI dosing improves both GERD symptoms and asthma in children. These results will have broad applicability because patients possessing significant *CYP2C19* variants are a sizeable segment of the population. In fact, only about 40% of the population has the 'normal' (wildtype) metabolizer phenotype, while poor/intermediate (IM/PM), extensive (EM) and ultra-rapid (UM) metabolizer phenotypes make up 24%, 24% and 4% of the population, respectively (2).

2.2.5. Rationale for five diplotypes/phenotypes and dosing adjustment

The *CYP2C19* diplotypes and metabolizer phenotypes to be studied are described in Table 1. The frequencies of common diplotypes in our previous study (3), which comprised mainly Caucasians (38%) and African Americans (50%) were: *1/*1, 28%; *1/*n, 28%; and *1/*17, 34% where n refers to any of the loss-of-function SNPs. These were similar to previous reports. The frequencies of the less common diplotypes *2/*17 and *17/*17 were 5% and 3.5%, respectively (figure 3). If encountered, *2/*17 diplotype would be dosed as NM (no change from conventional) based on our prior figure 3 PK data. These data support the use of 5 distinct metabolizer phenotypes in children which warrant distinct dosing adjustments from the conventional two-tiered dosing. We have developed an evidenced-based dosing algorithm tailored to Extensive (EM), Ultra-rapid (UM), Intermediate (IM) and Poor metabolizers (PM) that is based on pediatric PK principles after analyzing the limited extant pediatric data (1). These estimates are also in agreement with that proposed by Furuta(78) but are as yet untested in children.

2.2.6. Pharmacokinetics of PPIs may also depend on *ABCB1* genotype

SNPs in *ABCB1,* which encodes MDR1 (P-glycoprotein, P-gp), an efflux transporter expressed in the small intestine, colon and other tissue (88), may also influence the PK and PD of PPIs, which are substrates for MDR1(89). Three common SNPs: C3435T (rs1045642), T1654C (rs1128503) (silent) and T2677G/A (rs2032582) have been reported to alter MDR1 expression and activity though results among studies are controversial (90). The C3435T SNP has been reported to influence the bioavailability of lansoprazole and other PPIs (89, 91-93) and possibly PPI pharmacodynamics (67) though more recent studies are controversial (94, 95). Genotyping *ABCB1* SNPs C3435T, T1654C, and T2677G/A captures a large portion of the observed haplotypes though haplotype association studies have been inconclusive (96). This project will explore the influence of genotypes and haplotyes of 3435/1654/2677 on the PK and PD of lansoprazole in children (all previous studies were done in adults). These studies are significant because they will identify whether common *ABCB1*SNPs need to be considered in guiding PPI dosing.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

Risks of Blood Drawing

There are small risks to blood sampling, usually some pain/discomfort with the blood stick and blood loss.

Risks of Study Drug

Lansoprazole has been approved by the FDA for the indications GERD, duodenal ulcers, H. pylori eradication, benign gastric ulcer, NSAID-associated gastric ulcer, eosinophilic esophagitis, and pathological hypersecretory conditions. It is approved by the FDA down to age 12 months. Lansoprazole has been used in >10,000 patients in phase II and III clinical trials involving varying doses and durations and have been found to be well-tolerated in both short-term and long-term trials. Rarely (~1% of cases) patients have reported diarrhea, constipation, abdominal pain, and nausea with use of Lansoprazole. There is a risk of increased respiratory infections at the current conventional dosing. The current FDA label for Lansoprazole states that PPI therapy may be associated with increased risk for Clostridium difficile associated diarrhea. Long-term and multiple daily dose PPI therapy may be associated with an increased risk of osteoporosis-related fractures of the hip, write or spine, and hypomagnesemia has been reported rarely with prolonged treatment.

The FDA does not recommend using lansoprazole for:

- indications beside the above conditions.
- children < 1 year of age.
- prolonged periods (> 3 months).

Risks of Study Participation. Participants in GenARA may be at risk for worsening of GERD symptoms. However, during the study all participants will be monitored closely for worsening of GERD symptoms by clinic and phone visits and there will be a GERD safety plan. The first management strategy recommended in the recent NASPGHAN expert guidelines for pediatric GERD includes very specific evidence-based modifications to diet and lifestyle (97, 98). All participants in the trial (regardless of randomization) will receive the intervention of education about diet and lifestyle modifications to reduce GERD symptoms. These therapies are outlined in the patient handout: *GERD in Children and Adolescents*, published jointly by the NASPGHAN and the American Academy of Pediatrics, which will be given to all subjects (see Appendix). Participants will also be monitored closely throughout the study for worsening of GERD symptoms. A GERD rescue plan has been developed with consultation from the study pediatric gastroenterologist (see Section 8.11 Justification for PPI placebo/GERD Safety Plan and Appendix: GERD Safety Plan) and includes non-PPI antacid remedies. For patients with mild GERD and some persisting degree of asthma symptoms (i.e., GenARA participants), there exists equipoise regarding the role of long-term PPI use. Participants randomized to PPI may have experienced improved asthma but there is an increased risk with long-term PPI use. Participants randomized to placebo may be more likely to have worsening of GERD and asthma symptoms but may also be at higher risk for adverse effects of long-term PPI use. Thus, use of a placebo-control with close safety monitoring in place is justifiable.

Overall, the risks of this trial are small due to the baseline disease severity of participants, the nature of the interventions, the risk reduction safeguards and the safety of the testing procedures.

Minimizing risk:

- We have minimized these risks by studying lansoprazole at a dose which is likely to reduce side-effects since we will be giving participants with slower metabolism a lower dose.
- We will review safety data with an independent Data & Safety Monitoring Committee, chaired by Dr. Christine Sorkness.
- We will follow participants closely with a daily diary card plan and frequent phone and clinic visits to assess for adverse events and worsening of asthma or GERD symptoms.
- Asthma and GERD safety plans have been developed to reduce the risk of SAEs.

2.3.2. Potential Benefits

Lansoprazole may improve GERD symptoms and asthma symptoms together and reduce the risk for asthma exacerbations. Although improvements to asthma are not proven, increase in asthma control and decrease risk of exacerbations are potential benefits for participants enrolled in the study who receive lansoprazole. Conclusions drawn from this study will benefit children with both GERD and asthma in the future through better understanding of dose response and characterization of the safety profile of lansoprazole. Research coordinator will also train the participant and caregiver how to detect respiratory tract illnesses and how to perform nasal secretion collection and storage. Participant Training: participant and caregiver will be trained on the format and expectations of documentation of the daily e-diary. Completion of the e-diary will include completion of daily asthma medication, daily study drug receipt, asthma symptoms and any adverse symptoms. The participant will also be given patient handout information on Asthma Management and Lifestyle interventions to help reduce GERD symptoms.
Research coordinators will perform lifestyle counseling to participant and caregivers regarding asthma management and management of GERD. Counseling may improve general health knowledge and self-management of asthma and GERD.

2.3.3. Compensation

Subjects will be fairly compensated for their time and effort. (maximum of $120)
At the end of the screening visit, all subjects will receive $20.
At the completion of a successful visit 2 (randomization), subjects will receive $50.
At the completion of visit 5, subjects will receive $50

3. Objectives

Primary: to determine if genotype-tailored PPI dosing significantly improves asthma symptoms in children with mild GERD and poorly controlled asthma.
Exploratory: to determine if genotype-tailored PPI dosing (a) significantly increases the risk for respiratory tract infection (RTI)

3.1. Study Outcome measures

3.1.1. Primary Outcome Measures

Primary Outcome: We will use the 'Juniper' **Asthma Control Questionnaire (ACQ)** as the primary outcome. It has been used in many well-designed multi-center asthma trials in adults and children (4, 99). This instrument has been validated for young school-age children and adults and used successfully in clinical trials with parents answering the questions for children younger than 11 years. The ACQ considers a broad set of common indicators of asthma control including use of bronchodilators, cough, nocturnal symptoms, level of activity, and pulmonary function. The ACQ is a good choice for primary outcome measure because: 1) it is a sensitive measure of asthma control (with a change of 0.4-0.5 in score reflecting a clinically meaningful difference in asthma control), 2) it is validated for children and adults in Spanish and English, and 3) its simplicity. Authorization for use has been obtained in advance from Professor Juniper.

3.1.2. Secondary Outcome Measures

- Change in GSAS, ASUI;
- Annualized rate of exacerbations, EPAC, RTI;

3.1.2.1. GERD Symptom Assessment Questionnaire Score (GSAS)

GERD symptoms will be measured using the Pediatric GERD Symptom Assessment Questionnaire (GSAS) which is a 10-item tool[40] that has been validated in children in the assessment of gastroesophageal reflux disease related symptoms such as chest/abdominal pain, pain/choking with eating, swallowing dysfunction, regurgitation and nausea. It assesses symptom frequency and severity from the previous 7-days on an 8-point scale with 0 and 7 indicating the least and greatest severity, respectively. Use of the GSAS has informed the cut-off 15 or greater as having significant GERD symptoms (44). We chose a maximum value of 80 for inclusion on account of this was 2 SD from the mean GSAS for untreated children without baseline GERD(4, 100).

3.1.2.2. Asthma Symptom Utility Index (ASUI)

ASUI will measure changes in asthma control.

3.1.2.3. Annualized rate of asthma exacerbations

An exacerbation will be defined per the recommendations of the NIH Asthma Exacerbation Taskforce (101) and will be defined as a worsening of asthma requiring the use of a systemic corticosteroid (at least 3 days of prednisolone/ prednisone or ≥1 days of dexamethasone) to prevent asthma worsening. Families will be encouraged to call the GenARA research coordinator with any increase in asthma symptoms. Management of asthma symptoms and criteria for initiating SABA and/or oral steroids are outlined in detail in the Appendix: Safety Plan for GenARA participants who experience increased asthma symptoms. If a subject seeks care outside of the GenARAtrial and receives oral steroids for asthma exacerbation this will be recorded as an exacerbation.

3.1.2.4. Annualized rate of Episodes of Poor Asthma Control (EPAC)

A study EPAC will be present if the participant meets any of the following criteria, (1) addition of systemic corticosteroid medication for asthma as above, (2) any unscheduled visit to a non-study related health care provider (ED, urgent care, hospital) for asthma symptoms, (3) increased use of rescue SABA by more than 4 additional puffs (or more than 2 additional nebulization) above baseline amount determined at enrollment.

3.1.2.5. Annualized rate of respiratory tract infection (RTI). Participant/caregiver report

Participants will be asked to document symptoms of RTI on daily diary cards per consensus definitions (102, 103). RTI symptoms will include: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) fever, feels hot, or has chills; (5) sore throat; and (6) sneezing. We used definitions of respiratory tract illness that have been previously used in pediatric studies and has been adapted from the literature by an expert panel (103-106). An RTI will be defined as two symptoms for at least one full day or one symptom for two consecutive days (107). Structured phone follow-up visits and in-person clinical visits will occur every 4 weeks and will assess and document inter-current incidence of RTI, in a manner similar to what we have used in past pediatric trials (4). Past studies have shown that patients can reliably recall respiratory symptoms over several weeks (4, 108).

3.1.2.6. Lung Function Testing

We will use an approved spirometric system, which will be appropriately calibrated, and procedures conducted per American Thoracic Society standards (109). Outcomes will include forced vital capacity (FVC), forced expiratory volume 1 second (FEV1), and FEV_1/FVC. Raw data and percent predicted values will be recorded and based on

accepted normative data. Percent predicted values will be computed using the same predicted lung function equations used in table 3 below in accordance with the NIH-AsthmaNet consortium.

Table 3: Predicted Lung Function Equations

Race/Ethnicity Designation	Age 5	Age 6-12	13 or older
Black	Female: Caucasian x .85* Male: Caucasian x .91*	African American**	African American#
Caucasian	Caucasian*	Caucasian**	Caucasian#
Asian	Caucasian x .88*	Caucasian x .88**	Caucasian x .88#
Hispanic	Caucasian*	Hispanic***	Mexican American#

*Eigen, Bieler, Grant, Christoph, Terrill, Heilman, Ambrosius, Tepper. Spirometric pulmonary function in healthy preschool children. Am J Respir Crit Care Med 2001;163:619-23.
** Wang, Dockery, Wypij, Fay, Ferris. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993;15:75-88.
*** Hsu, Jenkins, Hsi, Bourhofer, Thompson, Tanakowa, Hsieh. Ventilatory functions of normal children and young adults – Mexican-American, white, and black. I. Spirometry. Pediatrics. 1979; 95(1):14-23.
#Hankinson, Odencrantz, Fedan. Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 1999; 159:179-87.

4. Study Design

We propose a 24-week prospective, randomized, blinded trial in 6–17-year-old children with inadequately controlled asthma and recent evidence of mild GERD symptoms (fig 5). At visit 1, saliva will be collected to isolate DNA and determine *CYP2C19* genotype as previously described (3, 87). Genotyping will take place at Nemours Jacksonville under the direction of Drs. Mougey and Lima. Each participant's metabolizer phenotype will be determined within 5 business days and classified according to table 1. These data will be entered into the secure Duke REDCap database (116) and shared with the respective research coordinator (Duke or Jacksonville).
Following a 2-week run-in to demonstrate study adherence, participants will undergo randomization. Participants will be randomized to either genotype-tailored PPI dosing or matched placebo for the 24-week intervention.

Participants will have close follow-up via phone visits (figure 5). The primary outcome during the intervention period will be change in Asthma Control Questionnaire (ACQ) at 6 months.
Lansoprazole will be provided by CutisPharma, Inc.

5. Study Population:

5.1. Selection of the study population

Participants will be offered enrollment into the study via Institutional Review Board-approved methods including review of clinic schedules within the PI's division and by IRB-approved advertisements.

Consent: The study will be explained to the participant and caregiver by IRB-approved study staff (Principal Investigator, Co-Investigator, research coordinator or research assistant). Consent will be obtained by study staff specifically trained in obtaining consent. For children age 12-17, assent will also be obtained.

5.2. Enrollment Criteria

5.2.1. Inclusion Criteria

- Documented informed consent from legal guardian prior to study procedures
- Access to an iOS or Android enabled smartphone or tablet.
- Age: 6–17-year-old with documented clinician-diagnosed asthma
- Evidence of recent uncontrolled asthma (must meet at least one of the following). This convention for defining poorly controlled asthma has been successfully used in a large pediatric trial (4).
    - ACQ > 1.25
    - Use of short-acting beta-agonist for asthma symptoms twice/week or more on average over the past month
    - Nocturnal awakenings with asthma symptoms more than once per week on average over the last month
    - Two or more emergency department visits, unscheduled provider visits, prednisone courses or hospitalizations for asthma in the past 12 months
- Currently on dose of daily inhaled corticosteroid medication (ICS) for asthma control equivalent to 88mcg of fluticasone or greater for at least 6 weeks from the time of enrollment. Participant must be on NAEPP controller step 2-5 (5). Must be taking on average > 2 days/week.
- Currently with mild GERD symptoms (15>GSAS<80)(6) reported at V1. GSAS ranges from 0 to >440. A score of 80 was felt to be a conservation cut-off as it corresponds to + 2 SD above the mean GSAS score for adolescents with asthma without a previous diagnosis of GERD (4, 100).

5.2.2. Exclusion Criteria

- Taking daily *CYP2C19* substrates, inducers or inhibitors medication (see Appendix for CYP2C19 substrates, inducers, inhibitors);
- Past or current history of severe GERD or related disorders (erosive esophagitis, peptic ulcer disease, eosinophilic esophagitis) which in the opinion of the pediatric gastroenterology safety specialist/study physician requires treatment with acid-blocking agents.
- Daily use (7 days/week) of a PPI for more than 4 consecutive weeks (or > 12 total weeks) in the 6 months.
- previous intubation for asthma,
- Previous surgery involving the esophagus or stomach (anti-reflux surgery, peptic ulcer surgery, trachea-esophageal fistula repair)
- Forced expiratory volume in 1 second (FEV1) < 60% of predicted at enrollment.
- Any major chronic illness in the opinion of the PI that would interfere with participation in the intervention or completion of the study procedures.

- Current pregnancy, or recent pregnancy and currently lactating; females enrolled must agree to practice an adequate birth control method (abstinence, combination, barrier/spermicide, OCP) for the duration of the study.
- History of phenylketonuria (PKU);
- Medication use: treatment of GERD symptoms with over-the-counter antacids four days/week or more on average over past month.
- Theophylline preparations, azoles, anti-coagulants (warfarin/Coumadin), Atazanavir, Tacrolimus, methotrexate, insulin for Type 1 diabetes, digitalis, oral iron supplements when administered for iron deficiency within 1 month.
- Any investigational drugs within the past 30 days.
- Drug Allergies: previous allergic reaction from lansoprazole or other proton pump inhibitor medication or adverse reaction to aspartame; benzyl alcohol, corn starch, hydroxyethylcellulose, saccharin sodium, simethicone emulsion, sodium bicarbonate, sodium citrate (dihydrate), sorbitol solution, and sucralose.
- Inability to complete study procedures in a satisfactory manner according to the judgment of the research coordinator or PI.
- Less than 70% completion of all fields of daily diary (for asthma symptoms, SABA use and ICS medication adherence) during the run-in period; run-in can be extended by 1-2 weeks at the discretion of the site PI.
- Plan for family to move from study location within the next 6 months.

5.2.3. Exclusion considerations

We have designed inclusion/exclusion criteria with help from pediatric experts in asthma and GERD to reduce risk. Children with poor lung function (<60% FEV1), past significant acid-related disease (erosive esophagitis, peptic ulcer disease, eosinophilic esophagitis), current GSAS > 80 at visit 1, or use of daily PPIs in past 12 months as defined above will not be enrolled. Children with a GSAS >80 after visit 1 will be given education about GERD symptoms and management and managed per the GERD Safety plan (see appendices). All enrollees at the first visit will have a thorough medical evaluation. Children who are found to have significant medical problems (chronic disease that would affect participation or acute disease requiring attention) will not be enrolled but instead will be triaged for appropriate care by Dr. Lang. If GSAS score becomes > 150, the case will be reviewed with the pediatric GI consultant for management.

5.2.4. Inclusion of females and minorities

No racial/ethnic groups or genders will be excluded from either aim. Past asthma trials in children at the Nemours Jacksonville and DUMC sites have recruited high proportions of African American and Hispanic/Latino children.

5.25. Screen Failure

Subject can re-enroll after 30 days of screen fail. Study staff will assign new study ID numbers after subject has been re-enrolled. Screen Failure: Generally, a screen failure will be someone who consented to participate in research but who was disqualified during screening procedures for various reasons, documented during the screening process. Reasons for the participant to fail screening may include, but are not limited to, the participant not meeting inclusion criteria or meeting exclusion criteria (ineligibility). Participants who screen fail can be considered for re-enrollment after 30 days of the initial screen. Study staff will assign a new study ID to these participants.

5.3. Treatment Assignment Procedures

5.3.1. Additional Participant Enrollment

If a participant is randomized (see 5.3.2) and does not receive more than 1 week of study drug, then an additional replacement participant may be enrolled.

5.3.2. Randomization procedures

Participants who satisfy all eligibility criteria will be randomized 1:1 (lansoprazole: placebo).

The participant's randomized treatment assignment will be obtained through the Duke REDCap enrollment/randomization system. Randomization will occur at visit 2. At visit 2, the research staff will complete a randomization eligibility form and enter it into a secure internet web form created by IT/Bioinformatics at the Duke Office of Clinical Research. The randomization sequence will be stratified by clinical center in permuted blocks sizes with assignment ratios of 1:1. The treatment assignment number given to the participant will be associated with a specific drug kit. The study pharmacist at Duke will then make up the drug kit in a just-in-time fashion and provide a 30-day supply which will be rapid-shipped to the family.

The randomization visit must capture and document:

Confirmation of participant's eligibility for randomization
Confirmation of participant's legal consent
Completion of the randomization eligibility form by trained staff
Documentation in REDCap of a body weight
Documentation in REDCap of a valid and best address to overnight-ship study drug.

If a participant is randomized but does not receive study drug, that participant will not count towards total sample size and will be replaced by a new participant who, in turn, will be assigned a new identification number and receive treatment corresponding to the new identification number. The reason for not dosing the participant will be noted on the CRF.

Randomization: will occur at the end of the run-in period at Visit 2 and will occur roughly 14 days following visit 1. The range can be between 10 – 17 days. The purpose of this visit will be to evaluate the participant's adherence to study procedures, establish that the participant continues to be interested in participating in the study, establish that the patient meets all inclusion and exclusion criteria for randomization, undergo randomization, undergo further training on study procedures (e-diary, spirometry, study drug handling, study drug dosing, follow-up planning) and give monetary compensation. Randomization: trained research staff will complete a randomization checklist to confirm the participant meets criteria for randomization. These will include adherence to the e-diary, desire to remain in the study, no new health-related conditions exclusionary to randomization, confirmation that the family plans to remains in the area for study duration, no exacerbations of asthma and no significant changes in GER symptoms during run-in. Once study staff has confirmed that the participant is eligible for randomization, the research staff will sign-in to REDCap to look up and write down the participant's randomization drug code ID and metabolizer phenotype on the randomization form. All randomization drug code IDs will have 5-6 digits. The randomization drug code will correspond to the drug kits that will be shipped to the home.

Communication Procedures

Metabolizer phenotype determination: based on CYP2C19 genotyping procedures performed at Nemours Jacksonville, each participant will be assigned a metabolizer phenotype:
Each participant will have a metabolizer phenotype assigned by Dr. Mougey by 5 business days following visit 1. The metabolizer phenotype will be entered by Dr. Mougey or assistant into the HIPAA-compliant GenARA REDCap-based study database (116).

Table 4: phenotypes	
UM (5)	Ultra-rapid
EM (4)	Extensive
NM (3)	Normal
IM (2)	Intermediate
PM (1)	Poor

5.3.3. Masking Procedures

Participants, their families, and the study team will be blinded to the treatment assignment of PPI vs. placebo. Placebo will include the same suspension plus an inert corn-starch to maintain similar taste and consistency. Both active commercially available Lansoprazole and placebo liquid will be manufactured and supplied by Cutis Pharma, Inc. The pharmacy at the Duke site will prepare and dispense the study drug into a 30-day supply and will include a pre-marked syringe showing the appropriate individualized dosing.

5.3.4. Reasons for Participant Withdrawal

The study clinician may choose to suspend study drug dosing for up to 48 hours for any reason.

The investigator will withdraw a participant from receiving further study interventions if:

Any clinically significant adverse event (AE) is deemed by the principal investigator to require discontinuation of study drug.

Unmasking of the participant is performed. All intentional unmasking events should be recorded on a protocol deviation form in REDCap within 24 hours of the unmasking. The decision to unmask will be made in consultation with the Study PI if possible. The unmasked participant will be followed for safety for 7 days after the last dose and complete all remaining follow up assessments unless consent has been withdrawn.

Requested by the FDA, Sponsor or DMC.

Before discontinuing a participant from the study drug, the local investigator must contact the Study PI except in emergency situations.

The participant's parent or guardian may withdraw voluntarily from participation in the study at any time. The participant's parent or guardian is not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the study team on an event report form.

If a participant withdraws from treatment for any reason, we will attempt to continue them in the remaining study procedures (visits and all subsequent testing and follow-up). This is voluntary and will not occur if the participant withdraws consent.

Unmasking Procedure: Contact information: call the 24/7 number (Duke PI) at 919-717-9960 for ALL emergency unmasking requests. .

5.3.5. Termination of Study

This study may be terminated at any time by FDA or the Investigational New Drug Application (IND) sponsor under advisement of the Data Monitoring Committee (DMC).

6. Study Procedures

6.1. Summary of Procedures

Table 5: Summary of Procedures								
Visit	**V1**	**V2**	P1	**TH V3**	P2	**TH V4**	P3	**TH V5**
Time (weeks)***	0	2	6	10	14	18	22	26
Consent/(assent)	x							
Screening	x							
Baseline Hx	x							
Saliva for genotyping	x							
Lifestyle counseling[1]	x	x						
Urine pregnancy testing*		x						
Randomization		x						
Physical exam	x							
E-Diary training (or retraining)	x	x		x		x		
Spirometry	x	x		x[a]		x[a]		x[a]
E-Diary adherence assessment		x		x		x		x
Health history[2]		x	x	x	x	x	x	x
Med adherence			x	x	x	x	x	x
Con meds	x	x		x		x		x
Asthma Questionnaires[3]	x	x	x	x	x	x	x	x
GSAS	x			x		x		x
Adverse events	x	x	x	x	x	x	x	x
Reimbursement	x	x		x		x		x
Discharge								x

1 – asthma and GERD counseling
2 – clinical evaluation with physical examination can be performed as needed at the discretion of the site PI to evaluate adverse events or problems with asthma or reflux symptoms
3 – ACQ6, ASUI, Duke Asthma Score
GSAS=GERD symptom assessment Score
*-for females of childbearing potential.
*** optimal visit windows are +/- 5 days; window can be extended at the discretion of the PI
a- home spirometry
TH – telehealth visits over Maestro

6.2. Screening

Participants will be recruited through IRB approved methods including flyers, paid advertisements, clinic visits and telephone calls to established patients.

6.2.1. Run-in

The run-in period will begin following the end of visit 1 if the participant meets all criteria for inclusion into the study. The run-in period will be planned for 2 weeks. During this time the participant will continue his/her daily asthma medications as prescribed by his/her treating physician. The participant will begin completing daily diary cards to monitor asthma symptoms and to ensure that asthma control is reasonably stable. The participant and caregiver will be advised to call the study team in the event of any health problems. The participant will be advised to complete diary cards on daily basis and to not complete them all at once, or to complete them days at a time. Participants will not be able to be randomized if diary card

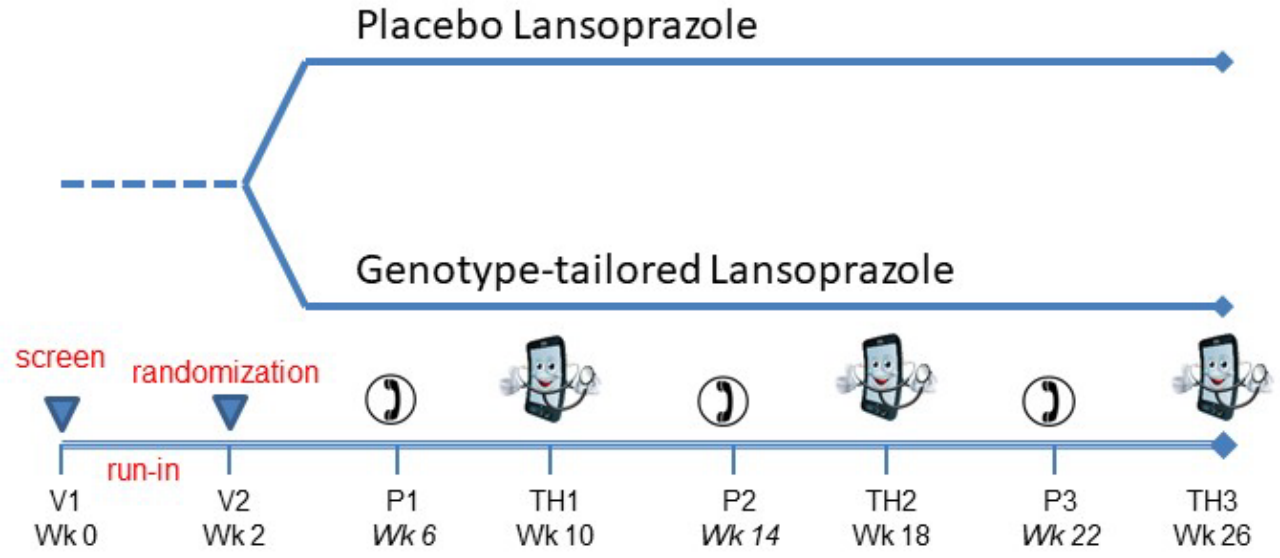
completion is not satisfactory. Less than 75% completion of daily diary for asthma symptoms,

SABA use and ICS medication adherence during the run-in period will prompt an extension of the run-in for an additional 1-2 weeks at the discretion of the investigator. Participants will also be asked to perform spirometry utilizing the VitalFlo spirometer and app daily.

6.3. Baseline Assessments and Training

6.3.1. Baseline Assessments: Visit 1

i. the study physician or nurse practitioner will complete the baseline physical exam form.
ii. the RC will complete ATS-approved spirometry. Spirometry data can be abstracted from participant record if already conducted on day of Visit 1.
iii. Baseline Asthma and Medical Directed Interview (with concomitant medications).
iv. Saliva Collection for Genotyping
v. Questionnaires directed by trained research coordinators.
    1. Asthma Control Questionnaire (ACQ)
    2. Asthma Symptom Utility Index (ASUI)
    3. Duke Asthma Score (DAS)
    4. GERD Symptom Assessment Score (GSAS)
vi. VitalFlo Mobile App training (with spirometry training)



Consent/assent Eligibility Hx/PE Genotype Questionnaires E-diary training PFT	Eligibility (RND) Questionnaires Randomization PFT	Adherence counseling Adverse events	Adherence counseling Adverse events Questionnaires PFT	Adherence counseling Adverse events	Adherence counseling Adverse events Questionnaires PFT	Adherence counseling Adverse events	Adherence counseling Adverse events Questionnaires PFT

Figure 5. Study schema. 26-week randomized blinded placebo controlled intervention trial. A 2-week run-in will ensure adherence to study procedures prior to randomization. All participants will receive their first month supply of study medication (and all subsequent month supplies) by mail. All participants will receive basic asthma education and evidence-based GERD lifestyle counseling at V1.

Saliva collection for DNA isolation: Saliva will be collected into a special saliva kit called the Oragene•DISCOVER (OGR-500) (2 ml sample volume)

Figure 6: Samples will be sent by overnight shipping to Nemours-Jacksonville:

Care of:
Edward B. Mougey, Ph.D.
Nemours Pharmacogenetics Center
Nemours Children's Clinic
807 Children's Way
Jacksonville, FL 32207

Office: 904.697.3781
Cell: 904.803.9011
Email 1: emougey@nemours.org
Email 2: emougey@vzw.blackberry.net

See Appendix for procedure and handling (Oragene Saliva Collection Appendix). Briefly, the procedure to collect saliva goes as follows: (1) explain the procedure to the participant. (2) the participant holds the funnel close to the mouth and carefully spits saliva into the funnel until the amount of liquid (not including bubbles) reaches the fill line on the funnel, (3) make sure the funnel stays upright and use one hand to stabilize the funnel, while the other hand carefully folds the lid closed. With closure the lid will snap into place. With closure, the liquid in the lid will mix with the saliva. Make sure the lid is closed tightly, (4) keep the tube upright and unscrew the funnel from the tube, (5) use the small cap to close the tube tightly, (6) make sure the cap is on tight before shaking vigorously for 5 seconds. All saliva samples from Duke and Jacksonville will be processed in the Jacksonville-based Nemours Pharmacogenomics Center. The saliva sample in the Oragene collection tube is stable for >12 months at room temperature. Drs. Mougey and Lima will oversee final determination of the metabolizer phenotype for each participant.

Genotyping. We will identify common gain-of-function and loss- of-function SNPs for ***CYP2C19***. Samples will be interrogated, and study personnel will be informed using the secure REDCap database. We have used this method previously (3) and reported the allele frequencies for the *2, *3, *8. *9, and *17 in pediatric and adult populations with asthma. These frequencies are shown above in table 1 and are similar to that reported in the literature (59, 60, 117). Briefly, *CYP2C19* SNPs will be interrogated using commercially available Taq-Man assays run in a 384 well ViiA 7 real-time qPCR instrument (both from Life Technologies, Carlsbad California). The 5 µL TaqMan assay contains 2.5 µL of 2X TaqMan genotyping master mix, 0.13 µL of 40X TaqMan probe, and 10 ng of genomic DNA. The cycle program used is a modified version of the manufactures recommended cycling program that involves: Stage 1, 60ºC for 30 seconds; Stage 2, 95ºC for 10 minutes; Stage 3, 70 cycles of 96ºC for 15 seconds, then 60ºC for 1 minute; Stage 4, 60ºC for 30 seconds). ***ABCB1*** SNPs: C3435T (rs1045642), T1654C (rs1128503) (silent) and T2677G/A (rs2032582) will be genotyped using TaqMan and Hardy-Weinberg Equilibrium will be evaluated.

Data Entry: During the run-in period, the research coordinator or trained support staff will enter all demographic questionnaire and V1 PFT data into REDCap. REDCap forms will notify which forms need to be entered in real time. It is very important for each clinical site to enter the address that the participant wants to receive the study drug. This address must be entered prior to randomization so that the Duke Investigational Drug Service can prepare and send the first month's supply of study drug. Daily home PFT data and daily e-diary data will be automatically captured.

Baseline Training: Visit 1 VitalFlo spirometry and App: At visit 1, after the participant has been determined to meet eligibility for entering the run-in the participant and guardian will be trained on how to download and use the vitalflo mobile app for recording daily study drug adherence, recording daily respiratory symptoms, and recording exacerbation events. They will also be taught how to use the Bluetooth connected home spirometer.

VitalFlo Spirometer

The VitalFlo spirometer is a compact, portable, home-based spirometer approximately the size of an inhaler that pairs with a smartphone app. The device uses an energy conserving turbine. Exhaled air flow causes the turbine to rotate, generating a voltage analogous to the rate of air flow across the turbine. The spirometer measures Forced expiratory volume in 1 second (FEV1), or the volume of air that is exhaled in the first second. The device prompts the user to perform a minimum of three expiratory maneuvers in and records the best of the three maneuvers. The information generated is collected on a microprocessor and then transmitted by a low power Bluetooth radio to the VitalFlo App (password protected) on the user's iPhone. The user is alerted, by the App, if their expiratory effort is inadequate (such as early termination of exhalation) and is provided coaching for proper technique. The data is then transmitted to a HIPAA-compliant cloud database. Participants will receive a survey after each time they measure lung function to gather information about any asthma symptoms they are experiencing. Investigators will ask that they use the VitalFlo spirometer prior to using albuterol for symptoms if possible. VitalFlo will also track, via cloud databases, outdoor temperature, humidity, air quality, and pollen counts: all environmental factors that can influence asthma symptoms. Routine calibration is not needed. The eventual goal of VitalFlo use is to identify drops in lung function preceding asthma symptoms to allow persons with asthma to intervene with rescue medications early in hopes of preventing progression to a more serious exacerbation of asthma ("red zone") requiring healthcare utilization, such as emergency care or hospitalization.

Participants will be given the VitalFlo spirometer after receiving instruction on proper use of the device. Participants will be asked to use the VitalFlo spirometer three times a week either in the morning or in the evening time. Investigators will use the morning and evening measurements to calculate the mean FEV1 for the day. After performing the spirometry maneuver, the user will be prompted to answer questions about their asthma symptoms. The lung function measurements and responses to the questions will be transmitted to a cloud-based HIPAA-compliant database and will be available for the investigators to download. Changes in lung function will be matched to subject-reported asthma symptoms and/or albuterol use.

Daily E-diary Questions Sent via the VitalFlo App

Duke GenARA Daily E-Questionnaire
1. Did you take your GenARA medication today? ☐ Yes ☐ No
2. Do you have cold or respiratory infection symptoms? ☐ Yes ▪ If yes, proceed to Q2A ☐ No ▪ If no, proceed to Q3 2A. Which of the following symptoms do you have? (Choose all that apply) ☐ Runny/stuffy nose ☐ Sore or itchy throat ☐ Headache ☐ Fever ☐ Cough
3. Did you have any daytime or nighttime asthma symptoms in the last 24 hours? ☐ Yes ▪ If yes, proceed to Q3A ☐ No ▪ If no, proceed to Q4 3A. Which of the following asthma symptoms do you have? (Choose all that apply) ☐ Shortness of breath ☐ Wheezing/whistling in the chest ☐ Coughing ☐ Chest tightness ☐ I needed albuterol
4. Since the last time you took the survey, did you experience any of the following? (Choose all that apply) ☐ Used an oral steroid for asthma ☐ Went to my doctor for asthma ☐ Went to the Emergency Room for asthma ☐ None of the above

During the run-in period between Visit 1 and Visit 2, participants will be expected to complete spirometry and e-diary questions each day. The vitalFlo mobile app will signal when the diary questions are ready and will prompt the participant to complete three forced expiratory maneuvers.

6.3.2. Baseline Assessments: Visit 2

i. The RC will complete ATS-approved spirometry
ii. Randomization eligibility form
iii. Questionnaires directed by trained research coordinators.
    a. Asthma Control Questionnaire (ACQ)
    b. Asthma Symptom Utility Index (ASUI)
    c. Duke Asthma Score (DAS)
iv. Randomize (if eligible) (see randomization procedure above)
v. Confirm appropriate mailing address

Baseline Training: Visit 2

VitalFlo spirometry and App: At visit 2, the research staff will review the daily adherence data from during the run-in period to determine if the participant is eligible for randomization. The participant and guardian will be given a brief refresher training on how to use the vitalflo mobile app for recording daily study drug adherence, recording daily respiratory symptoms, and recording exacerbation events.

After randomization at Visit 2, participants will be expected to complete the e-diary questions each day. The vitalFlo mobile app will signal when the diary questions are ready and will prompt the participant to complete spirometry (three forced expiratory maneuvers) once per week.

If a participant fails to complete more than 2 of 7 surveys in a week, they will be contacted by phone to attempt to recover missing data from that week. They will be asked about genara medication adherence, SABA use, presence of asthma symptoms, need for systemic corticosteroids and any need for urgent healthcare for asthma.

6.3.3. Follow-up Procedures

Will occur according to the procedures table 5 and figure 5. See below (section 6.5) for details of testing procedures.

a. Follow up Telehealth/videoVisits (week 10, 18, 24)

i. Home Spirometry witnessed by video (week 10, 18, 26)
ii. Concomitant medications
iii. Adherence assessment and counseling
iv. Questionnaires directed by trained research coordinators.

a. Asthma Control Questionnaire (ACQ)
b. Asthma Symptom Utility Index (ASUI)
c. Duke Asthma Score (DAS)
d. GERD Symptom Assessment Score (GSAS)
e. Adverse Events
f. Premature Withdrawal: We will request that the participant voluntarily return for a final termination phone visit. This visit will aim to be similar to the study completion phone visit (visit 5). The purpose of this visit will also be to evaluate general health and Asthma and GERD symptoms, and to ascertain any problems related to the request for withdrawal. Adverse event reporting will occur per protocol. We will recommend that the participant follow up in a timely manner with his/her primary care physician and asthma provider. If significant problems are present the PI/Study physician will facilitate the appropriate care – if needed, in consultation with the Genara Pediatric Gastroenterologist. We will also request that the participant return any unused study drug for appropriate destruction. The study physician/PI will also ensure that the participant has access to their normal controller and rescue asthma medications.

b. Interim Phone visits (weeks 6, 14, and 22)

i. Asthma Control Questionnaire6 (ACQ6)
ii. DAS interview
iii. Asthma Symptom Utility Index (ASUI)
iv. Concomitant medications

c. Final Visit. Study completion

i. End of Study procedures: preparation and mailing of un-blinding envelope to participant. Participants will receive a letter from the site PI and IND Sponsor (JL) regarding the participant's genotype with information and resources. The participant will be encouraged to share the letter with his/her doctor. Dispense monetary compensation.

7. Study Intervention/Product Description

All participants will have the intervention of lifestyle modification counseling which have been recommended in the pediatric GERD expert guidelines (97, 98). Participants will be randomized to receive either genotype-tailored once daily lansoprazole dosing or matched placebo according to table 6. The active lansoprazole and placebo will be provided by CutisPharma, Inc (Wilmington, MA). Each 5 FL OZ lansoprazole Compounding Kit is comprised of 0.45 grams of lansoprazole powder USP and 150 ml of PPI suspension containing artificial strawberry flavor. A research pharmacist will prepare blinded drug kits with individual dosing instructions (as shown here (https://www.youtube.com/watch?v=ANr_oZ-Bu6M). Premixed containers last for 30 days and will be shipped to participants between study visits. When compounded, the final product provides a homogeneous suspension containing 3mg/mL of lansoprazole in PPI Suspension comparable to the active ingredient contained in Simplified Lansoprazole Suspension (SLS). A matching placebo suspension with indistinguishable taste, color and viscosity will also be supplied by CutisPharma (see letter of support from CutisPharma, Inc.). The research pharmacist and trained research coordinator will instruct the caregiver on the exact daily volume amount. This approach will allow for genotype-tailored dosing.

7.1. Drug Administration

7.1.1. Drug will be given Once daily

Briefly, the compounding instructions are: (1) remove the cap from the bottle containing lansoprazole powder. Loosen powder inside. (2) Shake First PPI suspension for several seconds and then open bottle to pour out roughly 50% of the contents into the lansoprazole powder bottle. Make sure you are pouring liquid into solid. Re-cap the mixture and shake vigorously for 60 seconds. (3) Pour the remaining suspension into the lansoprazole powder bottle and shake again for 60 seconds. Make sure bottle is tightly capped.

7.1.2. Study Drug Delivery

Study drug will be sent from the Duke Investigational Drug Service (IDS) to the family's home address. The correct home address must be entered into REDCap prior to the randomization date. The pre-compounded study drug (either active drug or placebo) will be sent to each participant in a refrigerated container. Study drug will be sent to the family each 30 days. If there is a change in address, the individual clinical site coordinator is responsible for changing the preferred address in REDCap along with a notice by e-mail to GenARATeam@duke.edu).

7.1.3. Confirmation of Study Drug Receipt

Within 3 days of randomization, the participant's study coordinator should establish confirmation of receipt of study drug with the family. Once established, the coordinator will review with the participant and caregiver the proper dosing of the study drug. The study drug will come in a large bottle with instructions and a pre-marked syringe. Once there is confirmation that the participant has received the study drug and the coordinator has reviewed proper dosing instructions, the coordinator will enter confirmation of this into REDCap (in the study drug receipt field for visit 2).

Table 6: Genotype-guided Dosing Adjustments(1)

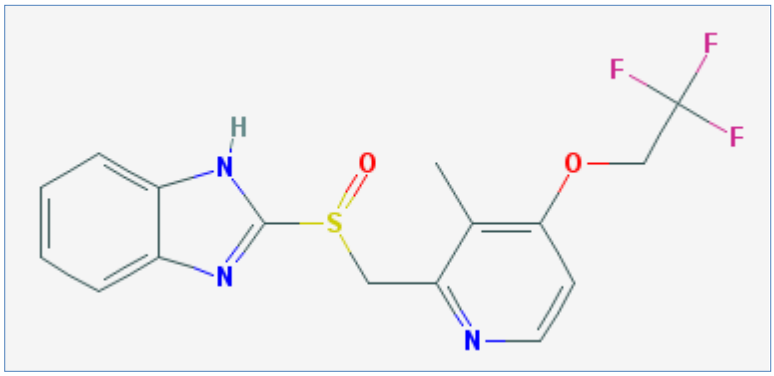
	Daily Dosing (and volume)		
phenotype	%change	<30kg	≥30kg
UM	100% ↑	30mg (10ml)	60mg (20ml)
EM	50% ↑	22.5mg (7.5ml)	45mg (15ml)
NM	0%	15mg (5ml)	30mg (10ml)
IM	30% ↓	10.5mg (3.5ml)	21mg (7ml)
PM	60% ↓	6mg (2ml)	12mg (4ml)

7.2. Investigational New Drug (IND): commercially available lansoprazole
Chemistry, Manufacturing, and Control Information (Drug/Active Ingredients, Pharmaceutical Class, Structural Formula, Formulation, Route of Administration). The drug to be used is a commercially available lansoprazole suspension under the Compounding Quality Act provided by a state licensed physician and compounded by a state licensed pharmacist. Drug/Active Ingredients: Each FIRST® - Lansoprazole Compounding Kit (5 FL OZ) is comprised of 0.45 grams of lansoprazole powder USP and 150 mL of FIRST® PPI (Proton Pump Inhibitor) suspension containing artificial strawberry flavor, benzyl alcohol, FD&C red# 40, hydroxyethylcellulose, purified water, saccharin sodium, simethicone emulsion, sodium bicarbonate, sodium citrate (dihydrate), sorbitol solution, and sucralose. This product contains ingredients that are derived from corn. When compounded, the final product provides a homogeneous suspension containing 3 mg per mL of lansoprazole in FIRST® PPI Suspension comparable to the active ingredient contained in Simplified Lansoprazole Suspension (SLS). First® Lansoprazole is marketed by CutisPharma, Inc, (Wilmington, MA).

Figure 7

Size	5 FL OZ
NDC#	65628-080-05
Lansoprazole Powder	0.45 g
FIRST – PPI Suspension	150 mL
PubChem CID	3883
Molecular Formula	$C_{16}H_{14}F_3N_3O_2S$
Molecular Weight	369.36147 g/mol
IUPAC Name:	2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole

Structure:



Proton Pump Inhibitor for oral administration: Labeling of Drug Product. For ages 6-17 years: Each label will provide the instructions: “Swallow directed dose once daily. Take at least 30 minutes before meal”. Also, all participants will be advised that study drug should be taken before eating. All labels also will include (1) subject identifier, (2) study identification, (3) instructions for administration, and (4) expiration date. Each study drug labels will consist of a 2-part tear off label. WARNING: ADAPTER CAP IS NOT CHILD-RESISTANT.

Handling of Study drug: FIRST®- Lansoprazole Compounding Kit components (un-mixed) have a two-year expiration date. Prior to compounding, store FIRST®- Lansoprazole Compounding Kit at room temperature 15°- 30°C (59°- 86°F). Based on real time temperature and humidity testing, compounded (mixed) FIRST®- Lansoprazole product is stable for at least 30 days at refrigerated temperature 2°-8°C (36° -46°F). Store the final compounded formulation at refrigerated temperature 2°-8°C (36°-46°F). For

oral use only. Avoid contact with eyes. Keep container tightly closed. Keep out of the reach of children. Protect from light. Protect from freezing. When compounded and stored according to instructions, acid neutralizing capacity is maintained for at least 30 days. The beyond-use date of the compounded product, as dispensed, when stored at refrigerated temperature is not later than 30 days.

7.3. Pharmacology and Toxicology Information

Mechanism of Action: Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H+/K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

Pharmacodynamics:

Antisecretory Activity: After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was greater than 3 and greater than 4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin. After the initial dose in that study, increased gastric pH was seen within 1 to 2 hours with 30 mg of lansoprazole and 2 to 3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1 to 2 hours post-dosing with 15 mg of lansoprazole. Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori* (*H. pylori*). The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of PREVACID given daily, twice daily and three times daily. The inhibition of gastric acid secretion as measured by intragastric pH gradually returned to normal over two to four days after multiple doses. There was no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) Cell Effects. During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

Other Gastric Effects in Humans. Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects. In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

Endocrine Effects. Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function. In 24-month carcinogenicity studies in Sprague-Dawley rats with daily lansoprazole dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rats.

Other Effects. No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems have been found in humans. Among 56 patients who had extensive baseline eye evaluations, no visual toxicity was observed after lansoprazole treatment (up to 180 mg/day) for up to 58 months. After lifetime lansoprazole exposure in rats, focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy were seen. *Microbiology:* Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the product label. *Helicobacter pylori Pretreatment Resistance.* Clarithromycin pretreatment resistance (≥2.0 mcg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95- 399).

Adverse Effects. There have been no reported cases of drug dependence or abuse involving proton pump inhibitors including Lansoprazole. There are also no radioactivity concerns. Adverse Reactions: Most commonly reported adverse reactions (≥1%): diarrhea, abdominal pain, nausea and constipation. Warnings & Precautions: Symptomatic response with Lansoprazole does not preclude the presence of gastric malignancy. PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.

Risk or Seriousness Anticipated: The possible risks and side effects observed in asthmatics treated with FIRST®Lansoprazole include the following: WARNINGS AND PRECAUTIONS: Bone fractures. People who are taking multiple daily doses of proton pump inhibitors for a long period of time may have an increased risk of fractures of the hip, wrist, or spine. Low magnesium levels in the body. This problem can be serious. Low magnesium can happen in some people who take proton pump inhibitors for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. Clostridium difficile-associated diarrhea. Long-term use of proton pump inhibitors may increase the risk of diarrhea caused by Clostridium difficile, especially in hospitalized patients.

Table 7: Drug Interactions	
Atazanavir	Do not co-administer with atazanavir.

Warfarin	Concomitant warfarin use may require monitoring for increases in INR and prothrombin time.
Tacrolimus	Concomitant tacrolimus use may increase tacrolimus whole blood concentrations.
Theophylline	Titration of theophylline dosage may be required when concomitant PREVACID use is started or stopped.
Methotrexate	FIRST Lansoprazole may increase serum levels of methotrexate.

8.Safety Procedures

8.1. Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Safety will be assessed from the initial study procedure at visit 1 through to the completion visit which will span roughly 26 weeks. Safety will be assessed by frequency and incidence of AEs and SAEs. A safety data monitoring committee (DMC) will be convened by Drs. Lang and Sorkness to review data and safety information from study participants throughout the study. A DMC charter will outline in detail the policies and procedures of the DMC (see Appendix).

8.2. Adverse Event

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. (Any change in clinical status, routine labs, x-rays, physical examinations, etc.), that is considered clinically significant by the study investigator is considered an AE.

8.3. Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, underlying disease processes or investigational plan.

8.4. Events of Special Interest

Unscheduled medical visit primarily for asthma, Acute Care/ED care for asthma, systemic steroids for asthma, hospitalization for asthma, Strep throat, pneumonia, ear infection, sinus infection, sore throat, acute RTI (any), upper respiratory tract infection (cold), diarrhea, gastroenteritis, fractures, and vomiting.

8.5. Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug, where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the drug caused the event? ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event. Therefore, **suspected adverse reaction** is any adverse event for which it appears more likely than not that the drug caused the adverse event. **Adverse reaction** is any adverse event caused by the drug. In cases where there is uncertainty, the site PI should seek council from the IND PI and DMC chair to determine.

8.5.1. Serious adverse event

or **serious suspected adverse reaction** or **serious adverse reaction** as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

- Death
- Life-threatening AE (“life-threatening” means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- Important medical event that may not result in one of the above outcomes, but in the judgement of the site PI may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

Any serious adverse event entered in the safety database will should elicit the research coordinator to notify the IND sponsor/PI by e-mail. The IND sponsor/PI will review all SAEs at the time that they are reported. Site Investigators must also submit safety reports locally as required by their local IRB.

8.6. Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

MILD: Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
MODERATE: Participant experiences enough symptoms or findings to require intervention
SEVERE: Participant experiences symptoms or findings that require significant intervention

Table 8: Definitions of Events for use in Genara Study	
Adverse Event	untoward medical occurrence in humans, whether or not considered drug/intervention-related
Unexpected	This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert or investigational plan
Reaction	Drug/intervention caused the adverse event *Suspected* – means there is a reasonable possibility
Serious	Event with death, that was life-threatening, or associated with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (can be related (reaction) or un-related (event) to intervention/drug)

8.7. Identification of Events and Timeframe for Reporting

As all participants in this study will have pre-existing medical conditions, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events. All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be reported in the hard copy and electronic case report form (REDCap). The investigator will provide the date of onset and resolution, intensity, frequency, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome.

8.8. Follow-up of Adverse Events

All events (study-related or not) must be followed until resolution, or if ongoing at the time of last safety contact, will be followed up to adequately evaluate the participant's safety or until the event stabilizes. All serious suspected adverse reactions and serious adverse reactions will be followed until resolution or until the patient is medically stable. All other events that cannot be resolved by 30 days after the safety monitoring period will be considered resolved by convention and entered in the electronic data capture (REDCap) system as such. Any event beginning more than 7 days after the last dose of study drug will not be captured.

8.9. Discontinuation of a Participant Due to Adverse Events

Participants may be withdrawn from the study at any time due to concerns about subject safety. Participants withdrawn from the study due to an AE (whether or not event was thought to be caused by intervention), whether serious or non-serious, must be followed by the investigator until the clinical outcome from the AE is determined. Any participant who experiences an AE may be withdrawn at any time from the study at the discretion of the investigator. The IND/protocol PI will seek input from DMC chair if needed. The AE(s) should be noted on the appropriate CRFs, and the participant's progress should be followed until the AE is resolved or considered stable. The IRB and DMC must be notified. If the AE may relate to overdose of study treatment, the package insert should be consulted for details of any specific actions to be taken.

8.10. Reporting Procedures

All adverse events will be entered into the safety data system within 7 days of identification (REDCap). Serious events will be entered into the data system within 48 hours of identification and reported to the IND/protocol PI. If there are any technical difficulties, the SAE will be reported by direct communication to the study PI. The study PI will notify the Chair of the DMC. **Reporting to the Duke IRB:**

Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm). Any event that: (1) involves harm, or an increased potential for harm, to one or more participant(s), or others, AND (2) is unexpected, AND (3) is related, or probably related, to study procedures will be reported to the Duke IRB within 5 days of discovery, or within 24 hours if an unforeseen death.

Study staff can find reporting requirements and criteria for reporting on the Genara REDCap site.

8.10.1. Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the DMC. The IND sponsor will submit expedited safety reports (e.g. IND safety reports) to the regulatory agencies (FDA, DMC, IRB) as necessary, and will inform the sub-investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB. Documentation of the submission and receipt by the IRB must be retained for each expedited safety report. All serious events irrespective of their designation as "related" (reactions) or "not related" (events) to study product(s) will be reported to the FDA at least annually in a summary format.

8.10.2. Safety Oversight

The DMC will review written serious adverse events on a quarterly basis. In addition, a qualified and experienced pediatric pulmonologist (IND Sponsor/PI) and gastroenterologist (Co-I) will serve as clinical monitors. The IND sponsor/PI will review all SAEs at the time they are reported. If safety concerns are identified, the PI may request a meeting of the DMC to review safety data. At a minimum, PI will comment on the outcomes of the SAE and causal relationship of the SAE to the study product. If no SAEs prompt review at an earlier time point, the DMC will review AEs and SAEs at the regularly scheduled annual meeting. Additionally, DMC will periodically review interim safety analyses. The DMC will convene and make recommendations on termination of the study based on review of safety reports and halting rules. The safety data will be compiled by the REDCap study support team. Based on the recommendations of the DMC, the IND sponsor will make a decision to terminate or continue the study.

8.11. Justification for PPI placebo/GERD Safety Plan

For patients with mild GERD and some persisting degree of asthma symptoms, there exists reasonable equipoise regarding the role of long-term PPI use, and thus use of a placebo-control with safety monitoring in place is justifiable. Current guidelines from the NAEPP and NASPGHAN recommend that clinicians consider use of a PPI in this setting. However, the FDA has published warnings about the chronic use of PPIs citing various side effects that appear to be higher in patients taking higher doses or for prolonged periods. The FDA has advised clinicians that longer use (>8-12 weeks) should be approached with caution. The FDA advises providers to consider a lower dose (than the conventional) or a shorter duration if possible. Currently, lansoprazole is not approved for treatment of GERD beyond the duration of 8 weeks (beyond 12 weeks in children 1-11 years). For patients with serious acid-related disorders, the risk-to-benefit ratio is often favorable, however the risk-benefit analysis for patients with mild GER and asthma is more difficult to determine and thus requires study. The first management strategy recommended in the recent NASPGHAN expert guidelines for pediatric GERD includes very specific evidence-based modifications to diet and lifestyle (97, 98). Thus, all participants in the trial (regardless of randomization) will receive the intervention of education about diet and lifestyle modifications. These therapies are outlined in the patient handout: *GERD in Children and Adolescents*, published jointly by the NASPGHAN and the American Academy of Pediatrics, which will be given to all subjects (see Appendix). Participants will also be monitored closely throughout the study for worsening of GERD symptoms. A GERD rescue plan has been developed with consultation from the study pediatric gastroenterologist (see Appendix: GERD Safety Plan).

8.12. Asthma Safety Parameters

8.12.1. Assessment and Documentation of Asthma Action Plan at Visit 1

8.12.2. Daily e-Diary documentation of medication adherence

8.12.3. Phone study visits and interim phone contacts to monitor asthma control

8.12.4. Plans for asthma worsening

Since all participants have asthma, it is expected that some exacerbations will occur over the 6-month intervention. During the study, participants will be able to seek care from their normal asthma physician. However, the study PI will be available 24/7 by cell phone for asthma problems and other clinical care questions. Trained research staff will review basic asthma education with each family which will include signs and symptoms of asthma. They will be given an asthma educational packet that will include directions on self-management of asthma symptoms and the indications for calling study staff right away for management (see Appendix for Asthma safety plan). Participants will be educated on how to complete daily diary cards to closely monitor for changes in asthma and educated on the indications for taking rescue albuterol. Participants will also be monitored by 4 clinic visits and 3 telephone visits during the trial. Phone visits will assess study adherence and will monitor for asthma symptoms. Pre-specified threshold criteria for starting oral steroids for an asthma exacerbation will also be in place consistent with past NIH-funded pediatric asthma trials.

8.13. GERD Safety Parameters

8.13.1. GERD non-pharmacologic management counseling (See Appendix: GERD educational handout)

8.13.2. Clinic visit and phone contacts to monitor GERD severity

8.13.3. Plans for GERD worsening

Since all participants have mild GERD, it is possible that some will experience worsening of symptoms over the 6-month intervention. A detailed GERD management plan has been developed. This will allow for management of mild breakthrough symptoms and rapid identification and management of more severe symptoms. Families will be given a GERD educational packet that will include directions on self-management and the use of over-the-counter Calcium Carbonate (OTC-CC) remedies if needed (see GERD safety plan in appendix). If GERD worsens, is not managed with the study drug and OTC-CC, and is affecting normal functioning, the family will be advised to call the study staff for management with Dr. Lang in consultation with the pediatric gastroenterology physician (JF). Pre-specified threshold criteria for un-blinding and study termination will be in place to allow prompt management. This will include GSAS>150 for 2 consecutive weeks and preference of the participant and/or caregiver to drop-out.

8.13.4. Additional protections for children

Participation in this trial for children with asthma and GERD will provide closer monitoring and education on self-management for these conditions than would be provided for non-participants.

9. Clinical monitoring

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and Duke sponsor standard operating procedures. The IND sponsor/PI will conduct a site-monitoring visit after the site has received IRB approval around the time of first enrollment. Additional site visits will occur on an ad-hoc basis. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

10. Data Analysis & Statistical Considerations

10.1. Analyses for Lansoprazole treatment effect

Descriptive data summaries of key outcomes will be performed throughout the study for safety monitoring and identification of outliers. We will employ means, ranges, and measures of variance by treatment group; box-plots by treatment group; and time plots of diary data by treatment group. The primary outcome will be the change from baseline in ACQ during the treatment period. The means during the baseline and treatment period are calculated from ACQ completed by each individual. A mid-point analysis will be completed on efficacy and safety outcomes (GSAS, RTI, AEs) and presented to an independent Data & Safety Monitoring Committee (DMC). We will use a multiple regression model to analyze the primary outcome to address the specific hypotheses of the study. Secondary analyses will include evaluation of the hypotheses outlined in the specific aims for other outcomes such as rate of exacerbations and EPACs, rate of RTI, GSAS score, and FEV1. The same analytic approach as outlined for the primary outcome will be used for the analysis of other outcomes. In addition, secondary analyses will explore other contrasts that are of interest, such as the effect of obesity status, age, and sex, though this will only be of secondary importance as we are not powering the study for these interactive effects. We will test for effect modification of outcomes by patient characteristics stated above by adding additional terms to the model and testing for significance of the coefficients and interactions with main effects. A preliminary analysis will be performed on all outcome measures to assess distribution and normality assumptions, identify outliers, and check for unusual patterns of longitudinal data. We will use transformations, as appropriate. Continuous measures that are not normally distributed or amenable to transformation will be analyzed as ranks or categorized and analyzed with logistic regression models for binary, ordered or multinomial outcomes using likelihood ratio tests and the same indicator variables and contrast as outlined above. All pre-specified outcomes will be analyzed by data analysts (JEL) to confirm that accuracy of data filters and coding routines. Data filtering routines analysis programs will be archived to allow future replication of our results. We will use the latest version of SAS 9.3 (SAS Institute, Inc, Cary NC).

10.2. Analyses of genotype/haplotype associations

Associations between lansoprazole and metabolite PK with *CYP2C19* genotype will be analyzed by additive, dominant or recessive models as previously described by our laboratory (118) using SAS 9.3 (Cary, NC). Associations between lansoprazole and metabolite PK with *ABCB1* SNPs (C3435T (rs1045642), T1654C (rs1128503) (silent) and T2677G/A (rs2032582)) and the 1236/2677/3435 haplotype will be analyzed similarly. General linear modeling will be performed and adjusted for age, race gender and *CYP2C19* diplotype. These analyses will complement the pop PK association analyses with genetic variation.

10.3. Sample size and Power calculations

The primary outcome for evaluation of power is change from baseline of ACQ. Based on our preliminary data in this exact patient population, we anticipate the mean ACQ at entry will be around 1.2, and a standard deviation of roughly 0.7 (based on Lang JE, *Thorax*, 2016) (45). Based on the differences in ACQ we saw between children without GERD symptoms and those with

Table 9: Sample Size Calculations

[13] *--Friday, July 29, 2016 --12:34:40*

t tests — Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size	
	Effect size d	= 0.7142857
	α err prob	= 0.05
	Power (1−β err prob)	= .9
	Allocation ratio N2/N1	= 1
Output:	Noncentrality parameter δ=3.3120065	
	Critical t	= 1.9886097
	Df	= 84
	Sample size group 1	= 43
	Sample size group 2	= 43
	Total sample size	= 86

mild GERD symptoms, we aim to detect an AQC change of 0.5. By using the ACQ (instead of ASUI) and assuming a two-tailed type 1 error rate of 5%, we will have improved power compared to using ASUI. Maintaining the goal of 110 randomizations, we can have an attrition rate of 20% (88 complete) and have a power of 90.6%. This assumes an intention to treat paradigm to the statistical analysis. Calculations were performed based on t-tests of independent means using G*Power Version 3.1.9.2 (Universitat Kiel, Germany).

11. Privacy, Data Storage & Confidentiality

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

11.1. Participant confidentiality

Participant confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests, in addition to the clinical information relating to participating participants. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Clinical study sites will permit access to such records. The principal investigator will ensure that the use and disclosure of personal health information obtained during this research study complies with the Federal Privacy Regulation. In the U.S., the Health Insurance and Portability and Accountability (HIPAA) Privacy Rule applies. The rule provides U.S. federal protection for the privacy of protected health information sent to or collected in the U.S. for the purposes of this research by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. "Authorization" is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the applicable Federal Privacy Regulations. The relevant privacy authorization will be combined in the informed consent document (approved by the IRB).

12. Quality Control and Quality Assurance

12.1. Data handling and record keeping

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable local laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all expedited safety reports. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Case report forms will be derived from the eCRFs and provided to the sites to record and maintain data for each participant enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original. Data reported in the eCRF should be consistent with the case report form/source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the case report forms and eCRFs.

12.2. Data Management Responsibilities

All case report forms, and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study. Duke for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

12.3. Data Capture Methods

Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant internet data entry system (REDCap) provided by the DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the case report forms/source documents.

12.4. Study Records Retention

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the investigator for at least 10 years after the end of the study or per local/state regulations or until participants reach 21 years, or applicable Federal laws, whichever is longer. No study records will be destroyed without prior authorization from the sponsor.

12.5. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1

5.2. Noncompliance, sections 5.20.1, and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the site PI and IND sponsor.

All deviations from the protocol must be addressed in study case report forms. A completed copy of the protocol deviation form must be maintained in the regulatory file and uploaded into REDCap. Protocol deviations must be submitted to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

13. Ethics/Protection of Human Participants

13.1. Ethical Standard

The investigator will ensure that the study will be conducted in accordance with the protocol, the ethical principles of Good Clinical Practice (ICH E6) that have their origin in the Declaration of Helsinki, and all applicable national and local regulations. The investigator will ensure that the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs.

13.2. Institutional Review Board

Prior to enrollment of participants into this trial, the protocol, the informed consent form, and any materials or advertisements presented to participants will be reviewed and approved by the appropriate IRB/REB. The responsible official for the IRB/REB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB/REB's composition and the institution's federal-wide assurance number (if applicable) will be provided to the DCC. If amendments to the protocol were required, the amendments will be written by the sponsor and provided to the investigator for submission and approval to the IRB/REB.

13.3. Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the participants and their families. Consent forms describing in detail the study procedures and risks are given to the participant's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the participant's legal guardian will be asked to read and review the document. Upon reviewing the document, a trained member of the study team will explain the research study to the participant's legal guardian and answer any questions that may arise. The participant/participant's legal guardian will sign the informed consent document prior to the conduct of any study procedures. The participant's legal guardian should have the opportunity to think about the study prior to agreeing to participate. The participant's legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to their legal guardian that the quality of their medical care will not be adversely affected if they decline to participate in this study. For non-English speakers, an interpreter will be provided to present the study, accompanied by a short form may be used to obtain informed consent.

The IND sponsor, or designee will provide the investigator, in writing, any new information that bears significantly on the participants' risk to receive the investigational product. This new information will be communicated by the investigator to participants' legal guardians who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participants' legal guardians will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the participant's legal guardian consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, informed consent must be obtained and properly executed.

By signing the informed consent form, the participant's legal guardian agrees that the participant will complete all evaluations required by the trial, unless the participant's legal guardian withdraws the participant voluntarily or the participant is withdrawn from the trial for any reason. The family will get a signed copy of the informed consent form and will be given contact information that will allow them to contact research staff (including coordinator 24-hour pager and PI cell phone) and Nemours or Duke IRB staff (as appropriate) at all hours.

Subject's Capacity to Give Legally Effective Consent: the GenARA study will include minors who cannot independently give legally effective consent. In these cases, inclusion will require parental permission/informed consent from a legal guardian. Assent will be required by children age 12 and up.

13.4. Recruitment

Recruitment will occur through IRB approved means.

13.5. Study Discontinuation

If the study is discontinued, enrolled participants will continue to be followed for safety assessments. All adverse events must be followed through resolution.

14. References:

1. Lima JJ, Franciosi JP. Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene-drug pairs. Pharmacogenomics. 2014;15(11):1405-16.
2. Strom CM, Goos D, Crossley B, Zhang K, Buller-Burkle A, Jarvis M, et al. Testing for variants in CYP2C19: population frequencies and testing experience in a clinical laboratory. Genet Med. 2012;14(1):95-100.
3. Lima JJ, Lang JE, Mougey EB, Blake KB, Gong Y, Holbrook JT, et al. Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. J Pediatr. 2013;163(3):686-91.
4. Writing Committee for the American Lung Association Asthma Clinical Research C, Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307(4):373-81.
5. NAEPP. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (Full Report 2007). NHLBI/NIH, US Department of Health and Human Services; 2007 August 28, 2007. Contract No.: NIH Publication No. 07-4051.
6. Lang JE, Hossain MJ, Lima JJ. Overweight children report qualitatively distinct asthma symptoms: Analysis of validated symptom measures. The Journal of allergy and clinical immunology. 2015.
7. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, et al. National surveillance of asthma: United States, 2001-2010. Vital & health statistics Series 3, Analytical and epidemiological studies / [US Dept. 2012(35):1-67.
8. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. The Journal of allergy and clinical immunology. 2014;134(3):547-53 e5.
9. Patel MR, Leo HL, Baptist AP, Cao Y, Brown RW. Asthma outcomes in children and adolescents with multiple morbidities: Findings from the National Health Interview Survey. The Journal of allergy and clinical immunology. 2014.
10. O'Byrne PM, Pedersen S, Schatz M, Thoren A, Ekholm E, Carlsson LG, et al. The poorly explored impact of uncontrolled asthma. Chest. 2013;143(2):511-23.
11. CDC. Asthma's Impact on the Nation: Data from the CDC National Asthma Control Program. In: National Center for Environmental Health DoEHaHE, editor. 2015.
12. Thakkar K, Boatright RO, Gilger MA, El-Serag HB. Gastroesophageal reflux and asthma in children: a systematic review. Pediatrics. 2010;125(4):e925-30.
13. Gunnbjornsdottir MI, Omenaas E, Gislason T, Norrman E, Olin AC, Jogi R, et al. Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. The European respiratory journal. 2004;24(1):116-21.
14. Kwiecien J, Machura E, Halkiewicz F, Karpe J. Clinical features of asthma in children differ with regard to the intensity of distal gastroesophageal acid reflux. J Asthma. 2011;48(4):366-73.
15. Huggins S. The role of gastroesophageal reflux disease in asthma. Journal of the American Academy of Nurse Practitioners. 2008;20(5):238-42.
16. Osler W. Bronchial asthma. The principles and practice of medicine. New York, NY: Appleton; 1892. p. 497-501.
17. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56(12):1654-64.
18. Irwin RS, Curley FJ, French CL. Difficult-to-control asthma. Contributing factors and outcome of a systematic management protocol. Chest. 1993;103(6):1662-9.
19. Richter JE. Gastroesophageal reflux disease and asthma: the two are directly related. The American journal of medicine. 2000;108 Suppl 4a:153S-8S.
20. Lopes FD, Alvarenga GS, Quiles R, Dorna MB, Vieira JE, Dolhnikoff M, et al. Pulmonary responses to tracheal or esophageal acidification in guinea pigs with airway inflammation. J Appl Physiol (1985). 2002;93(3):842-7.
21. Lang IM, Haworth ST, Medda BK, Roerig DL, Forster HV, Shaker R. Airway responses to esophageal acidification. Am J Physiol Regul Integr Comp Physiol. 2008;294(1):R211-9.
22. Hamamoto J, Kohrogi H, Kawano O, Iwagoe H, Fujii K, Hirata N, et al. Esophageal stimulation by hydrochloric acid causes neurogenic inflammation in the airways in guinea pigs. J Appl Physiol (1985). 1997;82(3):738-45.
23. Allen GB, Leclair TR, von Reyn J, Larrabee YC, Cloutier ME, Irvin CG, et al. Acid aspiration-induced airways hyperresponsiveness in mice. J Appl Physiol (1985). 2009;107(6):1763-70.
24. Harding SM, Schan CA, Guzzo MR, Alexander RW, Bradley LA, Richter JE. Gastroesophageal reflux-induced bronchoconstriction. Is microaspiration a factor? Chest. 1995;108(5):1220-7.
25. Wu DN, Tanifuji Y, Kobayashi H, Yamauchi K, Kato C, Suzuki K, et al. Effects of esophageal acid perfusion on airway hyperresponsiveness in patients with bronchial asthma. Chest. 2000;118(6):1553-6.
26. Herve P, Denjean A, Jian R, Simonneau G, Duroux P. Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. The American review of respiratory disease. 1986;134(5):986-9.
27. Patterson RN, Johnston BT, Ardill JE, Heaney LG, McGarvey LP. Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. Thorax. 2007;62(6):491-5.

28. Harding SM, Guzzo, M.R., Maples, R.V., Alexander, R.W., Richter, J.E. Gastroesophageal reflux induced bronchoconstriction vagolytic doses of atropine diminish airway responses to esophageal acid infusion. American journal of respiratory and critical care medicine. 1995;151:A589.
29. Mansfield LE, Hameister HH, Spaulding HS, Smith NJ, Glab N. The role of the vague nerve in airway narrowing caused by intraesophageal hydrochloric acid provocation and esophageal distention. Annals of allergy. 1981;47(6):431-4.
30. Zhu GC, Gao X, Wang ZG, Hu ZW, Zhang CC, Lai YG, et al. Experimental study for the mechanism of gastroesophageal-reflux-associated asthma. Dis Esophagus. 2014;27(4):318-24.
31. Andersen LI, Schmidt A, Bundgaard A. Pulmonary function and acid application in the esophagus. Chest. 1986;90(3):358-63.
32. Wright RA, Miller SA, Corsello BF. Acid-induced esophagobronchial-cardiac reflexes in humans. Gastroenterology. 1990;99(1):71-3.
33. Schan CA, Harding SM, Haile JM, Bradley LA, Richter JE. Gastroesophageal reflux-induced bronchoconstriction. An intraesophageal acid infusion study using state-of-the-art technology. Chest. 1994;106(3):731-7.
34. Harding SM, Guzzo MR, Richter JE. 24-h esophageal pH testing in asthmatics: respiratory symptom correlationwith esophageal acid events. Chest. 1999;115(3):654-9.
35. Oelschlager BK, Quiroga E, Parra JD, Cahill M, Polissar N, Pellegrini CA. Long-term outcomes after laparoscopic antireflux surgery. The American journal of gastroenterology. 2008;103(2):280-7; quiz 8.
36. Kaufman JA, Houghland JE, Quiroga E, Cahill M, Pellegrini CA, Oelschlager BK. Long-term outcomes of laparoscopic antireflux surgery for gastroesophageal reflux disease (GERD)-related airway disorder. Surgical endoscopy. 2006;20(12):1824-30.
37. Sontag SJ, O'Connell S, Khandelwal S, Greenlee H, Schnell T, Nemchausky B, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. The American journal of gastroenterology. 2003;98(5):987-99.
38. Larrain A, Carrasco E, Galleguillos F, Sepulveda R, Pope CE, 2nd. Medical and surgical treatment of nonallergic asthma associated with gastroesophageal reflux. Chest. 1991;99(6):1330-5.
39. Kiljander TO, Salomaa ER, Hietanen EK, Ovaska J, Helenius H, Liippo K. Gastroesophageal reflux and bronchial responsiveness: correlation and the effect of fundoplication. Respiration; international review of thoracic diseases. 2002;69(5):434-9.
40. Khoshoo V, Mohnot S, Haydel R, Jr., Saturno E, Edell D, Kobernick A. Bronchial hyperreactivity in non-atopic children with asthma and reflux: effect of anti-reflux treatment. Pediatric pulmonology. 2009;44(11):1070-4.
41. Khoshoo V, Haydel R, Jr. Effect of antireflux treatment on asthma exacerbations in nonatopic children. Journal of pediatric gastroenterology and nutrition. 2007;44(3):331-5.
42. dos Santos LH, Ribeiro IO, Sanchez PG, Hetzel JL, Felicetti JC, Cardoso PF. Evaluation of pantoprazol treatment response of patients with asthma and gastroesophageal reflux: a randomized prospective double-blind placebo-controlled study. J Bras Pneumol. 2007;33(2):119-27.
43. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. American journal of respiratory and critical care medicine. 2006;173(10):1091-7.
44. Lang JE, Hossain MJ, Lima JJ. Overweight children report qualitatively distinct asthma symptoms: analysis of validated symptom measures. J Allergy Clin Immunol. 2015;135(4):886-93 e3.
45. Lang JE, Hossain J, Holbrook JT, Teague WG, Gold BD, Wise RA, et al. Gastro-oesophageal reflux and worse asthma control in obese children: a case of symptom misattribution? Thorax. 2016;71(3):238-46.
46. Blake K, Teague WG. Gastroesophageal reflux disease and childhood asthma. Current opinion in pulmonary medicine. 2013;19(1):24-9.
47. Harding SM, Allen JE, Blumin JH, Warner EA, Pellegrini CA, Chan WW. Respiratory manifestations of gastroesophageal reflux disease. Annals of the New York Academy of Sciences. 2013;1300:43-52.
48. Ichikawa H, Sugimoto M, Sugimoto K, Andoh A, Furuta T. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. Journal of gastroenterology and hepatology. 2015.
49. Ward RM, Kearns GL. Proton pump inhibitors in pediatrics : mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. Paediatric drugs. 2013;15(2):119-31.
50. Sachs G, Shin JM, Briving C, Wallmark B, Hersey S. The pharmacology of the gastric acid pump: the H+,K+ ATPase. AnnuRev Pharmacol Toxicol. 1995;35:277-305.
51. Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors. Pharmacology and rationale for use in gastrointestinal disorders. Drugs. 1998;56(3):307-35.
52. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006;23 Suppl 2:2-8.
53. Hagymasi K, Mullner K, Herszenyi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors.

Pharmacogenomics. 2011;12(6):873-88.
54. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. European journal of clinical pharmacology. 2008;64(10):935-51.
55. Faure C, Michaud L, Shaghaghi EK, Popon M, Laurence M, Mougenot JF, et al. Lansoprazole in children: pharmacokinetics and efficacy in reflux oesophagitis. Aliment Pharmacol Ther. 2001;15(9):1397-402.
56. Gunasekaran T, Gupta S, Gremse D, Karol M, Pan WJ, Chiu YL, et al. Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability. J Pediatr Gastroenterol Nutr. 2002;35 Suppl 4:S327-S35.
57. Tran A, Rey E, Pons G, Pariente-Khayat A, D'Athis P, Sallerin V, et al. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. Clin Pharmacol Ther. 2002;71(5):359-67.
58. Litalien C, Theoret Y, Faure C. Pharmacokinetics of proton pump inhibitors in children. Clin Pharmacokinet. 2005;44(5):441-66.
59. Wedlund PJ. The CYP2C19 enzyme polymorphism. Pharmacology. 2000;61(3):174-83.
60. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet. 2002;41(12):913-58.
61. Fukushima-Uesaka H, Saito Y, Maekawa K, Ozawa S, Hasegawa R, Kajio H, et al. Genetic variations and haplotypes of CYP2C19 in a Japanese population. Drug Metab Pharmacokinet. 2005;20(4):300-7.
62. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clinical pharmacokinetics. 2002;41(12):913-58.
63. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. Jama. 2009;302(8):849-57.
64. Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clinical pharmacology and therapeutics. 2006;79(1):103-13.
65. Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther. 2006;79(1):103-13.
66. Kearns GL, Leeder JS, Gaedigk A. Impact of the CYP2C19*17 allele on the pharmacokinetics of omeprazole and pantoprazole in children: evidence for a differential effect. Drug Metab Dispos. 2010;38(6):894-7.
67. Gawronska-Szklarz B, Wrzesniewska J, Starzynska T, Pawlik A, Safranow K, Ferenc K, et al. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with Helicobacter pylori infection. Eur J Clin Pharmacol. 2005;61(5-6):375-9.
68. Hunfeld NG, Mathot RA, Touw DJ, van Schaik RH, Mulder PG, Franck PF, et al. Effect of CYP2C19*2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. Br J Clin Pharmacol. 2008;65(5):752-60.
69. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet. 2005;20(3):153-67.
70. Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. Pharmacogenomics. 2004;5(2):181-202.
71. Zhang D, Yang M, Liu M, Zhang Y, Wang X, Xiao X, et al. Pharmacokinetics of lansoprazole and its main metabolites after single intravenous doses in healthy Chinese subjects. Xenobiotica. 2012;42(11):1156-62.
72. Yacyshyn BR, Thomson AB. The clinical importance of proton pump inhibitor pharmacokinetics. Digestion. 2002;66(2):67-78.
73. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44(1):41-4.
74. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole--a gastric proton pump inhibitor--on pentagastrin stimulated acid secretion in man. Gut. 1983;24(4):270-6.
75. Stedman CA, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. Aliment Pharmacol Ther. 2000;14(8):963-78.
76. Wang L. Pharmacogenomics: a systems approach. Wiley Interdiscip Rev Syst Biol Med. 2010;2(1):3-22.
77. Serrano D, Torrado S, Torrado-Santiago S, Gisbert JP. The influence of CYP2C19 genetic polymorphism on the pharmacokinetics/- pharmacodynamics of proton pump inhibitor-containing Helicobacter pylori treatments. Curr Drug Metab. 2012;13(9):1303-12.
78. Furuta T, Sugimoto M, Shirai N. Individualized therapy for gastroesophageal reflux disease: potential impact of pharmacogenetic testing based on CYP2C19. Molecular diagnosis & therapy. 2012;16(4):223-34.
79. Furuta T, Shirai N, Xiao F, Ohashi K, Ishizaki T. Effect of high-dose lansoprazole on intragastic pH in subjects who are homozygous extensive metabolizers of cytochrome P4502C19. Clin Pharmacol Ther. 2001;70(5):484-92.

80. Ward RM, Tammara B, Sullivan SE, Stewart DL, Rath N, Meng X, et al. Single-dose, multiple-dose, and population pharmacokinetics of pantoprazole in neonates and preterm infants with a clinical diagnosis of gastroesophageal reflux disease (GERD). Eur J Clin Pharmacol. 2010;66(6):555-61.
81. Gumus E, Karaca O, Babaoglu MO, Baysoy G, Balamtekin N, Demir H, et al. Evaluation of lansoprazole as a probe for assessing cytochrome P450 2C19 activity and genotype-phenotype correlation in childhood. Eur J Clin Pharmacol. 2012;68(5):629-36.
82. Knebel W, Tammara B, Udata C, Comer G, Gastonguay MR, Meng X. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. J Clin Pharmacol. 2011;51(3):333-45.
83. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert review of clinical pharmacology. 2013;6(4):443-51.
84. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. The American journal of gastroenterology. 2012;107(7):1001-10.
85. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. The American journal of gastroenterology. 2012;107(7):1011-9.
86. de Jager CP, Wever PC, Gemen EF, van Oijen MG, van Gageldonk-Lafeber AB, Siersema PD, et al. Proton pump inhibitor therapy predisposes to community-acquired Streptococcus pneumoniae pneumonia. Alimentary pharmacology & therapeutics. 2012;36(10):941-9.
87. Lang JE, Holbrook JT, Mougey EB, Wei CY, Wise RA, Teague WG, et al. Lansoprazole is Associated with Worsening Asthma Control in Children with the CYP2C19 Poor Metabolizer Phenotype. Annals of the American Thoracic Society. 2015.
88. Kivisto KT, Niemi M, Fromm MF. Functional interaction of intestinal CYP3A4 and P-glycoprotein. Fundamental & clinical pharmacology. 2004;18(6):621-6.
89. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol. 2001;364(6):551-7.
90. Leschziner GD, Andrew T, Pirmohamed M, Johnson MR. ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research. Pharmacogenomics J. 2007;7(3):154-79.
91. Furuta T, Sugimoto M, Shirai N, Matsushita F, Nakajima H, Kumagai J, et al. Effect of MDR1 C3435T polymorphism on cure rates of Helicobacter pylori infection by triple therapy with lansoprazole, amoxicillin and clarithromycin in relation to CYP 2C19 genotypes and 23S rRNA genotypes of H. pylori. Aliment Pharmacol Ther. 2007;26(5):693-703.
92. Kodaira C, Sugimoto M, Nishino M, Yamade M, Shirai N, Uchida S, et al. Effect of MDR1 C3435T polymorphism on lansoprazole in healthy Japanese subjects. Eur J Clin Pharmacol. 2009;65(6):593-600.
93. Zhang YX, Wei SJ, Yang XY, Zhang WP, Wang XY, Dang HW. Effects of genetic polymorphisms of CYP2C19*2/*3 and MDR1 C3435T on the pharmacokinetics of lansoprazole in healthy Chinese subjects. Int J Clin Pharmacol Ther. 2014.
94. Li CY, Zhang J, Chu JH, Xu MJ, Ju WZ, Liu F, et al. A correlative study of polymorphisms of CYP2C19 and MDR1 C3435T with the pharmacokinetic profiles of lansoprazole and its main metabolites following single oral administration in healthy adult Chinese subjects. Eur J Drug Metab Pharmacokinet. 2013.
95. Li CY, Zhang J, Chu JH, Xu MJ, Ju WZ, Liu F, et al. A correlative study of polymorphisms of CYP2C19 and MDR1 C3435T with the pharmacokinetic profiles of lansoprazole and its main metabolites following single oral administration in healthy adult Chinese subjects. Eur J Drug Metab Pharmacokinet. 2014;39(2):121-8.
96. Hodges LM, Markova SM, Chinn LW, Gow JM, Kroetz DL, Klein TE, et al. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). Pharmacogenet Genomics. 2011;21(3):152-61.
97. Lightdale JR, Gremse DA. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013;131(5):e1684-95.
98. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Journal of pediatric gastroenterology and nutrition. 2009;49(4):498-547.
99. American Lung Association Asthma Clinical Research C, Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med. 2007;356(20):2027-39.
100. Lang JE, Hossain, J., Holbrook, J. T., Teague, W. G., Gold, B. G., Wise, R. A., Lima, J. J. Gastro-oesophageal reflux and worse asthma control in obese children: a case of symptom misattribution? Thorax. 2016;71:238-46.
101. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Jr., Gern J, et al. Asthma outcomes: exacerbations. The Journal of allergy and clinical immunology. 2012;129(3 Suppl):S34-48.
102. Lee GM, Salomon JA, Friedman JF, Hibberd PL, Ross-Degnan D, Zasloff E, et al. Illness transmission in the home: a possible role for alcohol-based hand gels. Pediatrics. 2005;115(4):852-60.
103. Sandora TJ, Taveras EM, Shih MC, Resnick EA, Lee GM, Ross-Degnan D, et al. A randomized, controlled trial of a multifaceted intervention including alcohol-based hand sanitizer and hand-hygiene education to reduce illness transmission in the

home. Pediatrics. 2005;116(3):587-94.
104. Butz AM, Larson E, Fosarelli P, Yolken R. Occurrence of infectious symptoms in children in day care homes. American journal of infection control. 1990;18(6):347-53.
105. Hendley JO, Gwaltney JM, Jr. Mechanisms of transmission of rhinovirus infections. Epidemiologic reviews. 1988;10:243-58.
106. Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiologic reviews. 1994;16(2):351-73.
107. Little P, Stuart B, Hobbs FD, Moore M, Barnett J, Popoola D, et al. An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial. Lancet. 2015;386(10004):1631-9.
108. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. BMJ (Clinical research ed. 1997;314(7082):722-7.
109. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107-36.
110. Zhang D, Wang X, Yang M, Wang G, Liu H. Effects of CYP2C19 polymorphism on the pharmacokinetics of lansoprazole and its main metabolites in healthy Chinese subjects. Xenobiotica. 2011;41(6):511-7.
111. Song M, Gao X, Hang T, Wen A. Simultaneous determination of lansoprazole and its metabolites 5'-hydroxy lansoprazole and lansoprazole sulphone in human plasma by LC-MS/MS: application to a pharmacokinetic study in healthy volunteers. J Pharm Biomed Anal. 2008;48(4):1181-6.
112. Chen ZY, Xie HT, Zheng QS, Sun RY, Hu G. Pharmacokinetic and pharmacodynamic population modeling of orally administered rabeprazole in healthy Chinese volunteers by the NONMEM method. Eur J Drug Metab Pharmacokinet. 2006;31(1):27-33.
113. Sheng YC, Wang K, He YC, Yang J, Zheng QS. Effect of CYP2C19 genotypes on the pharmacokinetic/pharmacodynamic relationship of rabeprazole after a single oral dose in healthy Chinese volunteers. Eur J Clin Pharmacol. 2010;66(11):1165-9.
114. Puchalski TA, Krzyzanski W, Blum RA, Jusko WJ. Pharmacodynamic modeling of lansoprazole using an indirect irreversible response model. J Clin Pharmacol. 2001;41(3):251-8.
115. Moore JG, Halberg F. Circadian rhythm of gastric acid secretion in men with active duodenal ulcer. Dig Dis Sci. 1986;31(11):1185-91.
116. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42(2):377-81.
117. Weitzel KW, Elsey AR, Langaee TY, Burkley B, Nessl DR, Obeng AO, et al. Clinical pharmacogenetics implementation: approaches, successes, and challenges. Am J Med Genet C Semin Med Genet. 2014;166C(1):56-67.
118. Mougey EB, Chen C, Tantisira KG, Blake KV, Peters SP, Wise RA, et al. Pharmacogenetics of asthma controller treatment. Pharmacogenomics J. 2013;13(3):242-50

Appendix B
SUBSTUDY: Asthma Medication Dosage

Step 2	Low Daily Dose	
Low dose ICS	**5-11 yo**	**Ages 12+**
Beclomethasone	**80-160**	**80-240**
Qvar 40	2-4 puffs daily	2-6 puffs daily
Qvar 80	1-2 puffs daily	1-3 puffs daily
Budesonide DPI	**180-360**	**180-540**
Pulmicort 90	2-4 puffs daily	2-6 puffs daily
Pulmicort 180	1-2 puffs daily	1-3 puffs daily
Ciclesonide MDI	**80-160**	**160-320**
Alvesco 80	1-2 puffs daily	2-4 puffs daily
Alvesco 160	1 puff daily	1-2 puffs daily
Flunisolide MDI	**160**	**320**
Aerospan 80	2 puffs daily	4 puffs daily
Fluticasone MDI	**88-176**	**88-264**
Flovent 44	2-4 puffs daily	2-6 puffs daily
Flovent 110	1 puff daily	1-2 puffs daily
Flovent 220		1 puff daily
Fluticasone Diskus	**100-200**	**100-300**
Flovent 50	2-4 puffs daily	2-6 puffs daily
Flovent 100	1-2 puffs daily	1-3 puffs daily
Flovent 250		1 puffs daily

Step 3	Low Daily Dose/LABA	
Low dose ICS + LABA	**5-11 yo**	**Ages 12+**
Fluticasone MDI	**100-200**	**100-300**
Advair 45	2-4 puffs daily	2-6 puffs
Advair 115	1 puff daily	1-2 puffs daily
Advair 230		1 puff daily
Fluciasone Diskus	**100-200**	**100-300**
Advair 100	1-2 puffs daily	1-3 puffs daily
Advair 250		1 puff daily
Advair 500		
Mometasone DPI	**110**	**110-220**
Asmanex Twisthaler 110	1 puff daily	1 -2 puffs daily
Asmanex Twisthaler 220		1 puff daily

Mometasone DPI	110	110-220
Dulura 100	1 puff daily	1 -2 puffs daily
Dulura 200		1 puff daily
Budesonide DPI	**180-360**	**180-540**
Symbicort 80/4.5	2-4 puffs	2-6 puffs daily
Symbicort 160/4.5	1-2 puffs	1-3 puffs

Step 3	Low Daily Dose	
Low dose ICS + Singulair	5-11 yo	Ages 12+
Beclomethasone	**80-160**	**80-240**
Qvar 40	2-4 puffs daily	2-6 puffs daily
Qvar 80	1 -2 puffs daily	1-3 puffs daily
Budesonide DPI	**180-360**	**180-540**
Pulmicort 90	2-4 puffs daily	2-6 puffs daily
Pulmicort 180	1-2 puffs daily	1-3 puffs daily
Ciclesonide MDI	**80-160**	**160-320**
Alvesco 80	1-2 puffs daily	2-4 puffs daily
Alvesco 160	1 puff daily	1-2 puffs daily
Flunisolide MDI	**160**	**320**
Aerospan 80	2 puffs daily	4 puffs daily
Fluticasone MDI	**88-176**	**88-264**
Flovent 44	2-4 puffs daily	2-6 puffs daily
Flovent 110	1 puff daily	1-2 puffs daily
Flovent 220		1 puff daily
Fluticasone Diskus	**100-200**	**100-300**
Flovent 50	2-4 puffs daily	2-6 puffs daily
Flovent 100	1-2 puffs daily	1-3 puffs daily
Flovent 250		1 puff daily

Step 3	Medium Daily Dose		High Daily Dose	
Medium/high dose ICS	Ages 5-11	Ages 12+	Ages 5-11	Ages 12+
Beclomethasone	**>160-320**	**>240-480**	**>320**	**>480**
Qvar 40	6-8 puffs daily	8-12 puffs daily		
Qvar 80	3-4 puffs daily	4-6 puffs daily	> 6 puffs daily	> 8 puffs daily
Budesonide DPI	**>360-720**	**>540-1080**	**>720**	**>1080**

Pulmicort 90	6-8 puffs daily			
Pulmicort 180	3-4 puffs daily	4-6 puffs daily	> 6 puffs daily	> 8 puffs daily
Ciclesonide MDI	**>160-320**	**>320-640**	**>320**	**>640**
Alvesco 80	3-4 puffs daily	6-8 puffs daily	> 6 puffs daily	
Alvesco 160	2 puffs daily	3-4 puffs daily	> 4 puffs daily	>6 puffs daily
Flunisolide MDI	**320-480**	**>320-640**	**>480**	**>640**
Aerospan 80	4-6 puffs daily	6-8 puffs daily	>8 puffs daily	> 10 puffs daily
Fluticasone MDI	**>176-352**	**>264-440**	**>352**	**>440**
Flovent 44	6-8 puffs daily			
Flovent 110	2-3 puffs daily	3-4 puffs daily	>4 puffs daily	>6 puffs daily
Flovent 220	1 puff daily	2 puffs daily	>2 puffs daily	>4 puffs daily
Fluticasone Diskus	**>200-400**	**>300-500**	**>400**	**>500**
Flovent 50	6-8 puffs daily			
Flovent 100	3-4 puffs daily	3-4 puffs daily	> 4 puffs daily	> 6 puffs daily
Flovent 250	1 puff daily	2 puffs daily	>2 puffs daily	> 4 puffs daily

Step 4	**Medium Daily Dose/LABA**	
Medium dose ICS + LABA	**Ages 5-11**	**Ages 12+**
Fluticasone MDI	**>200-400**	**>300-500**
Advair 45	6-8 puffs daily	
Advair 115	2-3 puff daily	3-4 puffs daily
Advair 230	1 puff daily	2 puffs daily
Fluciasone Diskus	**>200-400**	**>300-500**
Advair 100	3-4 puffs daily	4-5 puffs daily
Advair 250	1 puff daily	2 puff daily
Advair 500		1 puff daily
Mometasone DPI	**>220-440**	**>220-440**
Asmanex Twisthaler 110	2-4 puffs daily	2-4 puffs daily
Asmanex Twisthaler 220	1-2 puffs daily	1-2 puffs daily

Mometasone DPI	**>220-440**	**>220-440**
Dulura 100	2-4 puffs daily	2-4 puffs daily
Dulura 200	1-2 puffs daily	1-2 puffs daily
Budesonide DPI	**>360-720**	**>540-1080**
Symbicort 80/4.5	6-8 puffs daily	
Symbicort 160/4.5	3-4 puffs	4-6 puffs daily

Step 4	**Medium Daily Dose**	
Medium dose ICS + Singulair	**Ages 5-11**	**Ages 12+**
Beclomethasone	**>160-320**	**>240-480**
Qvar 40	6-8 puffs daily	8-12 puffs daily
Qvar 80	3-4 puffs daily	4-6 puffs daily
Budesonide DPI	**>360-720**	**>540-1080**
Pulmicort 90	6-8 puffs daily	
Pulmicort 180	3-4 puffs daily	4-6 puffs daily
Ciclesonide MDI	**>160-320**	**>320-640**
Alvesco 80	3-4 puffs daily	6-8 puffs daily
Alvesco 160	2 puffs daily	3-4 puffs daily
Flunisolide MDI	**320-480**	**>320-640**
Aerospan 80	4-6 puffs daily	6-8 puffs daily
Fluticasone MDI	**>176-352**	**>264-440**
Flovent 44	6-8 puffs daily	
Flovent 110	2-3 puffs daily	3-4 puffs daily
Flovent 220	1 puff daily	2 puffs daily
Fluticasone Diskus	**>200-400**	**>300-500**
Flovent 50	6-8 puffs daily	
Flovent 100	3-4 puffs daily	3-4 puffs daily
Flovent 250	1 puff daily	2 puffs daily

Step 5	**High Daily Dose/LABA**

High dose ICS + LABA	Ages 5-11	Ages 12+
Fluticasone MDI	**>400**	**>500**
Advair 45		
Advair 115	>4 puffs daily	>6 puffs daily
Advair 230	>2 puffs daily	>4 puffs daily
Fluciasone Diskus	**>400**	**>500**
Advair 100		
Advair 250	> 2 puff daily	> 2 puffs daily
Advair 500	> 1 puff daily	> 2 puff daily
Mometasone DPI	**>440**	**>440**
Asmanex Twisthaler 110		
Asmanex Twisthaler 220	>2 puffs daily	>2 puffs daily
Mometasone DPI	**>440**	**>440**
Dulura 100		
Dulura 200	>2 puffs daily	>2 puffs daily
Budesonide DPI	**>720**	**>1080**
Symbicort 80/4.5		
Symbicort 160/4.5		

Step 5	High Daily Dose	
High dose ICS + Singulair	**Ages 5-11**	**Ages 12+**
Beclomethasone	**>320**	**>480**
Qvar 40		
Qvar 80	> 6 puffs daily	> 8 puffs daily
Budesonide DPI	**>720**	**>1080**
Pulmicort 90		
Pulmicort 180	> 6 puffs daily	> 8 puffs daily
Ciclesonide MDI	**>320**	**>640**
Alvesco 80	> 6 puffs daily	
Alvesco 160	> 4 puffs daily	>6 puffs daily
Flunisolide MDI	**>480**	**>640**
Aerospan 80	>8 puffs daily	> 10 puffs daily

Fluticasone MDI	**>352**	**>440**
Flovent 44		
Flovent 110	>4 puffs daily	>6 puffs daily
Flovent 220	>2 puffs daily	>4 puffs daily
Fluticasone Diskus	**>400**	**>500**
Flovent 50		
Flovent 100	> 4 puffs daily	> 6 puffs daily
Flovent 250	>2 puffs daily	> 4 puffs daily

References

1. de-la-Coba C, Argüelles-Arias F, Martín-de-Argila C, et al. Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the Sociedad Española de Patología Digestiva. Rev Esp Enferm Dig (Madrid) 2016;108:207-24.
2. Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med 2016;176:238-46.
3. Lima JJ, Franciosi JP. Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene-drug pairs. Pharmacogenomics 2014;15:1405-16.
4. Strom CM, Goos D, Crossley B, et al. Testing for variants in CYP2C19: population frequencies and testing experience in a clinical laboratory. Genet Med 2012;14:95-100.
5. Lima JJ, Lang JE, Mougey EB, et al. Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. J Pediatr 2013;163:686-91.
6. Sachs G, Shin JM, Briving C, Wallmark B, Hersey S. The pharmacology of the gastric acid pump: the H+,K+ ATPase. AnnuRev Pharmacol Toxicol 1995;35:277-305.
7. Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors. Pharmacology and rationale for use in gastrointestinal disorders. Drugs 1998;56:307-35.
8. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 2006;23 Suppl 2:2-8.
9. Hagymasi K, Mullner K, Herszenyi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. Pharmacogenomics 2011;12:873-88.
10. Wedlund PJ. The CYP2C19 enzyme polymorphism. Pharmacology 2000;61:174-83.
11. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 2002;41:913-58.

12. Fukushima-Uesaka H, Saito Y, Maekawa K, et al. Genetic variations and haplotypes of CYP2C19 in a Japanese population. Drug Metab Pharmacokinet 2005;20:300-7.
13. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. Drugs 2003;63:2739-54.
14. Kita T, Sakaeda T, Baba T, et al. Different contribution of CYP2C19 in the in vitro metabolism of three proton pump inhibitors. Biol Pharm Bull 2003;26:386-90.
15. Sim SC, Risinger C, Dahl ML, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther 2006;79:103-13.
16. Kearns GL, Leeder JS, Gaedigk A. Impact of the CYP2C19*17 allele on the pharmacokinetics of omeprazole and pantoprazole in children: evidence for a differential effect. Drug Metab Dispos 2010;38:894-7.
17. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J Clin Pharmacol 2008;64:935-51.
18. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet 2005;20:153-67.
19. Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. Pharmacogenomics 2004;5:181-202.
20. Zhang D, Yang M, Liu M, et al. Pharmacokinetics of lansoprazole and its main metabolites after single intravenous doses in healthy Chinese subjects. Xenobiotica 2012;42:1156-62.
21. Sierra F, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther 2007;26:545-53.
22. Leonard CE, Freeman CP, Newcomb CW, et al. Proton pump inhibitors and traditional nonsteroidal anti-inflammatory drugs and the risk of acute interstitial nephritis and acute kidney injury. Pharmacoepidemiol Drug Saf 2012;21:1155-72.
23. Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis 2014;64:558-66.
24. Antoniou T, Macdonald EM, Hollands S, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open 2015;3:E166-71.
25. Peng YC, Lin CL, Yeh HZ, Chang CS, Wu YL, Kao CH. Association Between the Use of Proton Pump Inhibitors and the Risk of ESRD in Renal Diseases: A Population-Based, Case-Control Study. Medicine (Baltimore) 2016;95:e3363.
26. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. J Am Soc Nephrol 2016.
27. Nadri Q, Althaf MM. Granulomatous tubulointerstitial nephritis secondary to omeprazole. BMJ Case Rep 2014;2014.
28. Sampathkumar K, Ramalingam R, Prabakar A, Abraham A. Acute interstitial nephritis due to proton pump inhibitors. Indian J Nephrol 2013;23:304-7.
29. Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. Clin Gastroenterol Hepatol 2006;4:597-604.
30. Yang Y, George KC, Shang WF, Zeng R, Ge SW, Xu G. Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. Drug Des Devel Ther 2017;11:1291-9.
31. Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant 2017.
32. Holbrook JT, Wise RA, Gold BD, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA 2012;307:373-81.
33. Lang JE, Holbrook JT, Mougey EB, et al. Lansoprazole is Associated with Worsening Asthma Control in Children with the CYP2C19 Poor Metabolizer Phenotype. Annals of the American Thoracic Society 2015.

34. Lima JJ LJ, Mougey EB, Blake KB, Gong Y, Holbrook JT, Wise RA, Teague WG. Association of CYP2C19 Polymorphisms and Lansoprazole-Associated Respiratory Adverse Effects in Children. J Pediatr 2013.