CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209570Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader Review, Division Director, and Deputy Office Director Summary Review

Date	August 29, 2017
From	Thomas Smith, M.D., Sumathi Nambiar, M.D., M.P.H., and John Farley, M.D., M.P.H.
Subject	Combined Cross-Discipline Team Leader Review, Division Director, and Deputy Office Director Summary Review
NDA #	209570
Applicant	Chemo Research, S.L.
Date of Submission	December 29, 2016
PDUFA Goal Date	August 29, 2017
Non-Proprietary Name	Benznidazole
Dosage form / Strengths	Tablets: 100 mg, 12.5 mg
Applicant Proposed Indication/Population	Treatment of Chagas disease
Regulatory Action	Approval
Approved Indication/Population	Treatment of Chagas disease in pediatric patients 2 to 12 years of age

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Maria Allende, M.D.
Statistical Review	Felicia Griffin, Ph.D., and Janelle Charles, Ph.D.
Pharmacology Toxicology Review	James Wild, Ph.D.
OPQ Application Technical Lead	Dorota Matecka, Ph.D.
Microbiology Review	Shukal Bala, Ph.D.
Clinical Pharmacology Review	Abhay Joshi, Ph.D.
OPDP	Puja Shah, Pharm.D.
OSI	John Lee, M.D.
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DPMH	Jane Liedtka, M.D.

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DPVII= Division of Pharmacovigilance II
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CDRH/DMD=Center for Devices and Radiological Health/Division of Microbiology Devices
DPMH=Division of Pediatric and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

New Drug Application 209570 for benznidazole, an antiprotozoal agent, was submitted by Chemo Research, S.L., for the treatment of Chagas disease. The regulatory action is approval under Subpart H for the treatment of Chagas disease in pediatric patients 2 to 12 years of age.

Chagas disease, or American trypanosomiasis, is endemic throughout much of Mexico, Central America, and South America. It is caused by the protozoan *Trypanosoma cruzi*, which is most commonly transmitted by triatomine insect vectors. There are acute and chronic phases of infection. The acute phase is characterized by parasitemia which lasts 8 to 12 weeks. Symptoms are generally mild and nonspecific, and most acute infections are not diagnosed. Rare, severe manifestations of acute infection include meningoencephalitis or myocarditis. The host's immune response controls parasite replication, symptoms resolve, and patients enter into a chronic phase of infection which is lifelong. Most patients are asymptomatic (indeterminate), but approximately 20 to 30% have progression over years to decades to chronic Chagas cardiomyopathy or, less commonly, to gastrointestinal disease. The earliest signs of cardiac disease are conduction system abnormalities, usually right bundle branch block and/or left anterior fascicular block. Later manifestations include arrhythmias, apical aneurysms, thromboembolic phenomena, and dilated cardiomyopathy with congestive heart failure. Patients with advanced cardiomyopathy are at high risk of sudden death. There are no FDA-approved therapies for Chagas disease. Benznidazole and nifurtimox are available in the U.S. from the CDC.

The effectiveness of benznidazole for the treatment of Chagas disease in patients 6 to 12 years of age was established in two adequate and well-controlled trials. These trials demonstrated an effect on a surrogate endpoint, conversion to negative with nonconventional serologic assays, that is reasonably likely to predict clinical benefit in this population. The applicant provided data which were adequate to bridge the product used in these trials with the to-be-marketed product. Efficacy in children 2 to 5 years of age may be extrapolated from the data from older children. The course of Chagas disease and the effect of the drug are sufficiently similar in these populations, and the applicant presented information to support dosing and an acceptable safety profile for the younger age group. A nonrandomized, unblinded observational study evaluating long-term outcomes in adult patients with chronic Chagas disease treated with benznidazole has methodologic shortcomings and is not adequate to stand on its own as substantial evidence of efficacy in adult patients. (b) (4)

In the pediatric trials, the most common adverse reactions in patients treated with benznidazole were rash and abdominal pain. In a review of the literature, the most frequently reported adverse reactions associated with benznidazole are cutaneous reactions, gastrointestinal disorders, peripheral neuropathy, and paresthesia. Bone marrow depression has also been reported. Complete information on absorption, distribution, metabolism, and excretion (ADME) of benznidazole is not available. Benznidazole is potentially genotoxic and carcinogenic and, based on

animal studies, may cause fetal harm when administered to a pregnant woman. The Warnings and Precautions section of the label will contain information about the potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, hypersensitivity skin reactions, central and peripheral nervous system effects, and hematological manifestations of bone marrow depression.

The data submitted meet the evidentiary standard for a Subpart H approval of benznidazole for the treatment of Chagas disease in pediatric patients 2 to 12 years of age. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory prospective, single-arm, multicenter trial, with historical controls, to evaluate safety, efficacy and pharmacokinetics of benznidazole tablets for treatment of Chagas disease in children. Postmarketing requirements also include a human ADME/mass balance study to evaluate the routes and rates of benznidazole excretion, ascertain whether benznidazole has circulating drug metabolites, and if identified, evaluate the routes and rates of excretion for benznidazole metabolites, and a male rat fertility study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chagas disease, or American trypanosomiasis, is endemic throughout much of Mexico, Central America, and South America. It is caused by the protozoan *T. cruzi*, which is most commonly transmitted by triatomine insect vectors. • There are acute and chronic phases of infection. The acute phase is characterized by parasitemia which lasts 8 to 12 weeks. Symptoms are generally mild and nonspecific, and most acute infections are not diagnosed. Rare, severe manifestations of acute infection include meningoencephalitis or myocarditis. The host's immune response controls parasite replication, symptoms resolve, and patients enter into a chronic phase of infection which is lifelong. Most patients are asymptomatic (indeterminate), but approximately 20 to 30% have progression over years to decades to chronic Chagas cardiomyopathy or, less commonly, to gastrointestinal disease. The earliest signs of cardiac disease are conduction system abnormalities, usually right bundle branch block and/or left anterior fascicular block. Later manifestations include arrhythmias, apical aneurysms, thromboembolic phenomena, and dilated cardiomyopathy with congestive heart failure. Patients with advanced cardiomyopathy are at high risk of sudden death.	Chagas disease is a serious disease with potentially life-threatening complications. Although most patients are asymptomatic, approximately 20 to 30% have progression over years to decades to chronic Chagas cardiomyopathy or, less commonly, to gastrointestinal disease. Patients with advanced cardiomyopathy are at high risk of sudden death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no FDA-approved therapies for Chagas disease. • Benznidazole and nifurtimox are available in the U.S. from the Centers for Disease Control and Prevention (CDC).	There is an unmet medical need for therapies to treat Chagas disease.

Benefit	• The effectiveness of benznidazole for the treatment of Chagas disease in patients 6 to 12 years of age was established in two adequate and well-controlled trials using surrogate endpoints.
	  • de Andrade: This trial compared benznidazole, 7.5 mg/kg/day in two divided doses for 60 days, with placebo in the treatment of children 7 to 12 years of age with chronic indeterminate Chagas disease. The primary endpoint was the absence of specific antibodies at the end of the three-year follow-up period. A total of 129 patients were randomized and received treatment. At the end of follow-up, there was a significant difference between groups in the percentage of patients who became seronegative by a nonconventional AT ELISA: 35/64 (54.7%) in the benznidazole group vs. 3/65 (4.6%) in the placebo group.
	  • Sosa Estani: This trial compared benznidazole, 5 mg/kg/day in two divided doses for 60 days, with placebo in the treatment of children 6 to 12 years of age with chronic indeterminate Chagas disease. The primary endpoint was the proportion of children seronegative by conventional ELISA at the end of the four-year follow-up period. A total of 106 patients were randomized. At the end of follow-up, there was a significant difference between groups in the percentage of patients who became negative by a nonconventional F29 ELISA: 24/40 (60.0%) in the benznidazole group vs. 5/37 (13.5%) in the placebo group.
	These trials demonstrate an effect on a surrogate endpoint, conversion to negative with nonconventional serologic assays, that is reasonably likely to predict clinical benefit in this population.
		The data submitted meet the evidentiary standard for a Subpart H approval of benznidazole for the treatment of Chagas disease in pediatric patients 2 to 12 years of age. The trials demonstrated an effect on a surrogate endpoint, conversion to negative with nonconventional serologic assays, that is reasonably likely to predict clinical benefit in this population. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory prospective, single-arm, multicenter trial, with historical controls, to evaluate safety, efficacy and pharmacokinetics of benznidazole tablets for treatment of Chagas disease in children. The data submitted were not adequate to stand on their own as substantial evidence of efficacy in adult patients. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Efficacy in children 2 to 5 years of age was extrapolated from the data from older children. The course of Chagas disease and the effect of the drug are sufficiently similar in these populations, and the applicant presented information to support dosing and an acceptable safety profile for the younger age group. • Viotti: This was a nonrandomized, unblinded observational study comparing long-term outcomes in adult patients with chronic Chagas disease treated with benznidazole with outcomes in patients receiving no treatment. The primary outcome was disease progression, defined as a change to a more advanced Kuschnir group or death. The study population was 566 patients. Overall, 12 of 283 (4.2%) patients in the benznidazole group changed Kuschnir group compared with 41 of 283 (14.5%) patients in the untreated group. This study has methodologic shortcomings and is not adequate to stand on its own as substantial evidence of efficacy in adult patients. (b) (4)	
Risk	• In the pediatric trials, the most common adverse reactions in patients treated with benznidazole were rash and abdominal pain. • In a review of the literature, the most frequently reported adverse reactions associated with benznidazole are cutaneous reactions, gastrointestinal disorders, peripheral neuropathy, and paresthesia. Bone marrow depression has also been reported. • Benznidazole seems to be tolerated better in children than in adults. (b) (4) • Complete information on ADME of benznidazole is not available. • Benznidazole, a nitroimidazole, is contraindicated in patients who have taken disulfiram within the preceding two weeks. Consumption of alcohol or products containing propylene glycol may produce a disulfiram-like reaction in patients taking benznidazole. • Benznidazole is potentially genotoxic and carcinogenic and, based on	The safety information provided supports the use of benznidazole for the treatment of Chagas disease in pediatric patients 2 to 12 years of age. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	animal studies, may cause fetal harm when administered to a pregnant woman.	
Risk Management	• Postmarketing requirements include the accelerated approval confirmatory trial; a human ADME/mass balance study to evaluate the routes and rates of benznidazole excretion, ascertain whether benznidazole has circulating drug metabolites, and if identified, evaluate the routes and rates of excretion for benznidazole metabolites; and a male rat fertility study. • The Warnings and Precautions section of the label will contain information about the potential for genotoxicity and carcinogenicity, embryo-fetal toxicity, hypersensitivity skin reactions, central and peripheral nervous system effects, and hematological manifestations of bone marrow depression.	Postmarketing requirements will confirm the clinical benefit of benznidazole in pediatric patients, provide additional safety and pharmacokinetics information, and address remaining clinical pharmacology and pharmacology-toxicology issues. Routine pharmacovigilance activities will be adequate to monitor safety.

2. Background

New Drug Application 209570 for benznidazole, an antiprotozoal agent, was submitted by Chemo Research, S.L., for the treatment of Chagas disease. The applicant-proposed dosing regimen for (b) (4) (b) (4) (b) (4).

Chagas disease, or American trypanosomiasis, is endemic throughout much of Mexico, Central America, and South America. It is caused by the protozoan *T. cruzi*, which is most commonly transmitted by triatomine insect vectors. Vectors become infected by feeding on infected mammals. When they subsequently feed on uninfected hosts, the vectors excrete *T. cruzi* trypomastigotes in their feces. The trypomastigotes enter the host through breaks in the skin or through mucous membranes and invade nucleated cells. Trypomastigotes differentiate into intracellular amastigotes, which multiply by binary fission and differentiate into trypomastigotes, which are released into the circulation, invading new cells and providing a source for infection of new vectors. Additional mechanisms of transmission include congenital transmission, blood transfusions, organ transplantation, consumption of uncooked contaminated food, and laboratory exposure[1].

There are acute and chronic phases of infection. The acute phase is characterized by parasitemia which lasts 8 to 12 weeks. Symptoms are generally mild and nonspecific, and most acute infections are not diagnosed. Rare, severe manifestations of acute infection include meningoencephalitis or myocarditis. The host's immune response controls parasite replication, symptoms resolve, and patients enter into a chronic phase of infection which is lifelong. Most patients are asymptomatic (indeterminate), but approximately 20 to 30% have progression over years to decades to chronic Chagas cardiomyopathy or, less commonly, to gastrointestinal disease. The earliest signs of cardiac disease are conduction system abnormalities, usually right bundle branch block and/or left anterior fascicular block. Later manifestations include arrhythmias, apical aneurysms, thromboembolic phenomena, and dilated cardiomyopathy with congestive heart failure. Patients with advanced cardiomyopathy are at high risk of sudden death. Chagas gastrointestinal disease primarily affects the esophagus, colon, or both. Esophageal effects range from asymptomatic motility disorders to achalasia to megaesophagus. Colonic involvement may lead to megacolon. Chronic *T. cruzi* infection may reactivate in immunocompromised individuals such as organ transplant recipients and adults with human immunodeficiency virus (HIV) infection.

Diagnosis of acute Chagas disease depends on detection of circulating parasites. Methods include microscopy of fresh or Giemsa-stained peripheral blood smears, culture of whole blood in special media, or polymerase chain reaction (PCR) using whole blood. Diagnosis of chronic Chagas disease depends primarily on serologic methods. Serologic tests include enzyme-linked immunosorbent assays (ELISA), indirect immunofluorescence assays (IFA),

[1] Bern C. Chagas' disease. New Engl J Med 2015;373:456-66.

and indirect hemagglutination assays (IHA)[2]. These conventional assays detect primarily IgG antibodies using a complex mixture of parasite antigens or the entire parasite. Nonconventional ELISAs using recombinant proteins, purified antigens, or synthetic peptides are also available but are largely investigational. Nonconventional tests have increased specificity but may be less sensitive than conventional tests. The World Health Organization (WHO) considers a single positive conventional ELISA or IFA to be diagnostic of infection, but two tests are recommended for confirmation; if they are not in agreement, a third test (conventional or nonconventional) is recommended. PCR is of less value in the chronic phase of infection. The circulating parasite load is low, and sensitivity of the assay is variable. Negative PCR results do not prove the absence of infection.

There are no FDA-approved therapies for Chagas disease. Benznidazole is approved in other countries as monotherapy. In the early 1970s, Hoffman La-Roche (Roche) developed benznidazole and obtained registration of it in Brazil, Argentina, Bolivia, Uruguay, Peru, and Nicaragua as Radanil, Ragonil, or Rochagan, which are products for oral administration formulated in 100 mg and 50 mg uncoated scored tablets. In 2003, Roche donated all commercial rights and transferred the technology to manufacture benznidazole to the Brazilian government as a generic version of Roche's product, and, at the same time, Roche also withdrew its registration. The product was granted a marketing authorization by the Brazilian Drug Regulatory Authority (ANVISA) in November, 2006. Since that time, Laboratorio Farmacéutico de Pemambuco (LAFEPE), a Brazilian government manufacturing facility, has provided benznidazole to patients in Latin America. Another benznidazole product, Abarax, 100 mg and 50 mg tablets for oral administration, manufactured by Laboratorio ELEA, Buenos Aires, Argentina, has been approved in Argentina, Bolivia, Paraguay, and Chile in recent years (2012-2014) and is also available in Spain. In this NDA, the applicant submitted clinical trials in which patients were treated with either the Radanil product or the LAFEPE product. Thus, bridging the to-be-marketed product with products used in the clinical trials to support the NDA was an important review issue.

Benznidazole and nifurtimox, another drug used as monotherapy for the treatment of Chagas disease, are available in the U.S. from the Centers for Disease Control and Prevention (CDC)[3]. CDC recommends treatment for all cases of acute or reactivated Chagas disease and for chronic *T. cruzi* infection in children up to 18 years of age. CDC also recommends treatment for adults up to 50 years of age with chronic infection who do not have advanced Chagas cardiomyopathy. WHO recommends treatment for acute or reactivated Chagas disease and for patients with early chronic disease[4]. Congenital Chagas disease is considered acute disease.

The response to therapy is difficult to evaluate. Patients are considered cured only when previously positive conventional serologic tests become negative[2], which may take years to

[2] WHO Expert Committee on Control of Chagas Disease, 2002. Control of Chagas disease: second report of the WHO expert committee. World Health Organization, Geneva.
[3] Centers for Disease Control and Prevention, 2013. Parasites – American trypanosomiasis: antiparasitic treatment. Accessible at: https://www.cdc.gov/parasites/chagas/health_professionals/tx html
[4] World Health Organization, 2017. Chagas disease (American trypanosomiasis) fact sheet. Accessible at: http://www.who.int/mediacentre/factsheets/fs340/en/

decades; the time to seroreversion increases with increasing duration of infection. Spontaneous seroreversion to negative rarely occurs. The clinical outcomes of interest, cardiomyopathy or gastrointestinal disease, also take years to decades to develop.

A pre-IND meeting (PIND 118976) was held between Chemo Research and the Division of Anti-Infective Products (DAIP) on September 17, 2013. Chemo originally proposed an indication of "treatment of Chagas disease (b) (4) *Trypanosoma cruzi* (b) (4) (b) (4) (b) (4) DAIP recommended a longer-term trial with a serologic endpoint, expansion of the study population to include patients 0 to 3 years of age, and consideration of use of nifurtimox as a comparator. DAIP also recommended that Chemo obtain patient-level data from previous placebo-controlled trials of benznidazole in children.

Chemo was granted orphan drug designation for benznidazole for the treatment of Chagas disease on April 14, 2014. On August 20, 2015, the FDA added Chagas disease to the list of tropical diseases which are eligible for priority review vouchers (80 FR 50559).

An end-of-phase 2 meeting was held on April 27, 2016. Chemo proposed submitting source data from four clinical trials, two in the pediatric population and two in adults, along with findings from an observational study, systematic reviews of other studies in acute, congenital, and chronic Chagas disease. Chemo also proposed performing a post-approval PK/PD study. DAIP reiterated its recommendation to perform a pediatric trial.

A pre-NDA meeting was held on September 30, 2016. DAIP stated that the studies Chemo proposed to submit seemed to be adequate for review of an NDA and that as much source data as possible should be included.

NDA 209570 was submitted December 29, 2016, and contained publications or a study report along with source data from two pediatric trials (de Andrade[5] and Sosa Estani[6]) and two adult trials (Molina[7] and DNDi) which had benznidazole treatment arms. Chemo also provided reviews of published data on the use of benznidazole in acute, congenital, and chronic Chagas disease, a review of the use of benznidazole in children 6 years of age and under, an evaluation of RT-PCR in monitoring patients treated with benznidazole, and evidence to support *T. cruzi* serological and molecular assessments as biomarkers of clearance and reduction in disease

[5] de Andrade ALSS, Zicker F, de Oliveria RM, et al. Randomised trial of benznidazole in treatment of early *Trypanosoma cruzi* infection. Lancet 1996;348:1407-13.
[6] Sosa Estani S, Segura EL, Ruiz AM, et al. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. Am J Trop Med Hyg 1998;59:526-9.
[7] Molina I, Gomez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. New Engl J Med 2014;370:1899-908.

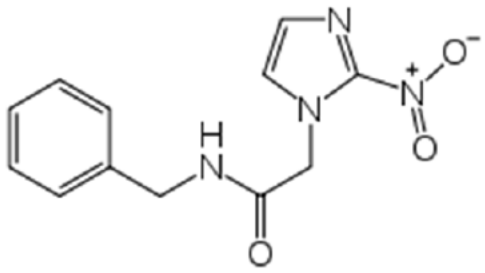
progression. Subsequently, source data were submitted from a study evaluating long-term outcomes of treating chronic Chagas disease in adults with benznidazole (Viotti[8]).

The applicant requested priority review designation and a tropical disease priority review voucher. Priority review designation was granted February 23, 2017, because Chagas disease is a rare disease, and until now, there are no approved drugs for it in the U.S. This is a 505(b)(2) application that relies in part on published literature for approval.

3. Product Quality

Dorota Matecka, Ph.D., was the application technical lead for the product quality assessment team. The team's findings are summarized below.

Benznidazole (N-benzyl-2-(2-nitro-1H-imidazol-1-yl) acetamide) has a molecular formula of $C_{12}H_{12}N_4O_3$; the molecular weight is 260.246 g/mol. The structural formula is:



Benznidazole drug substance is manufactured by [(b) (4)]. Chemistry, manufacturing, and controls information was provided by reference to DMF [(b) (4)] held by [(b) (4)]. The DMF was reviewed and found to be adequate. The drug substance specifications include tests and acceptance criteria for description, identification, water content, loss on drying, residue on ignition, heavy metals, assay, chromatographic purity, residual solvents, and particle size, and were found to be adequate. Drug substance batches manufactured by [(b) (4)] were used for clinical supplies and were found to be comparable to benznidazole batches manufactured by [(b) (4)]. Stability data support a retest period of [(b) (4)] when stored at [(b) (4)].

The tablet drug product manufacturer is Laboratorios Liconsa, S.A., Spain. Tablets are supplied in two strengths, 100 mg and 12.5 mg. Benznidazole 100 mg tablets are round, white, approximately 10 mm in diameter, scored twice as a cross on both sides, and debossed with "E" on each split portion. Benznidazole 12.5 mg tablets are round, white, approximately 5 mm in diameter, unscored, [(b) (4)], and debossed with "E" on one side. Inactive ingredients include pregelatinized corn starch, monohydrate lactose, sodium croscarmellose, microcrystalline cellulose, magnesium stearate, [(b) (4)] [(b) (4)]. The tablets can be [(b) (4)] made into a slurry for immediate

[8] Viotti R, Vigliano C, Lococo B, et al. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment. Ann Intern Med 2006;144:724-34.

administration to pediatric patients. The drug product specifications for the 12.5 mg and 100 mg tablets include tests and acceptance criteria for appearance, identification, uniformity of dosage units, assay, dissolution, (b) (4) time, (b) (4) purity, microbial limits, (b) (4) content. In addition, the specifications for the 100 mg tablet include tests for (b) (4) (b) (4). During the review, the drug product reviewers recommended several revisions to the specifications; the revised specifications were found to be adequate. The drug product will be packaged in white high density polyethylene bottles and closed with a (b) (4) cap. The 100 mg and 12.5 mg tablets will be packaged into 70 mL and 35 mL bottles, respectively, containing 100 tablets. Stability data support a shelf life of 24 months when stored at controlled room temperature 20°C to 25°C (68°F to 77°F). The manufacturer has committed to perform (b) (4).

The biopharmaceutics review found that the proposed dissolution method and revised acceptance criterion were acceptable.

The drug substance and drug product manufacturing and testing facilities were found to be acceptable.

The Office of Pharmaceutical Quality review team concluded that the applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product, benznidazole tablets. There are no unresolved product quality issues, and the team recommended approval.

4. Nonclinical Pharmacology/Toxicology

James Wild, Ph.D., was the pharmacology/toxicology reviewer for this application. His findings are summarized below.

In single oral dose toxicity studies in rats, benznidazole causes ultrastructural changes in the adrenal cortex, colon, esophagus, ovaries, and testis. In repeat oral dosing in dogs, neurotoxicity, including axonal degeneration and Purkinje cell degeneration was observed. Neurologic signs included apathy, hypertonia, hyperreflexia, ataxia, loss of balance, seizures, opisthotonos, and nystagmus. Neurotoxicity was not observed in other species.

Genotoxicity has been demonstrated in humans, in vitro in several bacterial species and mammalian cell systems, and in rodents. Benznidazole was mutagenic in several strains of *Salmonella typhimurium*, *Escherichia coli*, and *Klebsiella pneumoniae*. It was genotoxic in a chromosomal aberration assay in human lymphocytes and in sister chromatid exchange assays in human lymphocytes and in human Hep G2 cells. It was also genotoxic in a mouse bone marrow micronucleus assay, in mouse and human red blood cell micronucleus assays, in a mouse abnormal sperm head assay and in a human peripheral blood lymphocyte assay. A two-fold increase in chromosomal aberrations was reported in a study evaluating the cytogenetic effect of benznidazole in pediatric patients 11 months to 11 years of age with Chagas disease.

Carcinogenicity has been observed in mice and rats treated chronically with metronidazole, another nitroimidazole. It is not known whether benznidazole is associated with carcinogenicity in humans. Long-term carcinogenicity studies with benznidazole have not been performed.

Benznidazole was associated with fetal malformations when administered orally to pregnant rats and rabbits during organogenesis. In rats, anasarca, anophthalmia, and microphthalmia were observed at doses approximately 1 to 3 times the maximum recommended human dose (MRHD), and reduced maternal weights, and small litter sizes occurred at a dose approximately 3 times the MRHD. In rabbits, ventricular septal defects were observed at doses approximately 0.3 to 1 times the MRHD, and reduced maternal weight gain and abortions occurred at a dose approximately equal to the MRHD.

In a female fertility study in rats, orally administered benznidazole did not reduce pregnancy rates but there was increased post-implantation loss with lower live litter size at a dose approximately 3 times the MRHD.

In a pre-postnatal study in rats, cesarean section findings in first generation females born to dams administered benznidazole included higher pre-implantation loss, reduced corpora lutea counts and numbers of implantations and live embryos. Some first generation males had reduced testicular size and failed to mate or induce pregnancy. Mean values for mating performance, fertility index, testes weight, testes and epididymides sperm counts, and epididymal sperm motility and progression were unchanged. The no observed adverse effect level was considered to be 50 mg/kg/day, which is approximately equal to the MRHD.

In a chronic, repeated dosing study in male rats, benznidazole produced dose-dependent testicular and epididymal atrophy and aspermia at a dose approximately 0.6 times the MRHD. Fertility was not evaluated in this study. It is not known whether these effects are reversible. The applicant has agreed to conduct a postmarketing male fertility study in rats.

Dr. Wild concluded that this application was approvable from a pharmacology/toxicology perspective. Information about the potential for genotoxicity and carcinogenicity and embryofetal toxicity will be included in the Warnings and Precautions section of the label. Pregnancy testing and use of effective contraception will be recommended for females of reproductive potential. The male fertility study in rats is a postmarketing requirement.

5. Clinical Pharmacology

Abhay Joshi, Ph.D., was the primary clinical pharmacology reviewer for this application. The Office of Clinical Pharmacology (OCP) review team's findings and recommendations are summarized below.

Absolute bioavailability of benznidazole has not been determined. Pharmacokinetics are comparable among three formulations: a 100 mg tablet in a slurry, a 100 mg intact tablet, and eight 12.5 mg tablets in a slurry. There is no significant effect of food on exposure. Plasma protein binding is approximately 44%. The mean elimination half-life of benznidazole

following a single dose in healthy subjects is 12 to 13 hours. Body weight is a significant covariate on clearance (CL/F) of benznidazole. Body weight normalized CL/F is relatively greater in young children than in adults, and young children may require slightly higher mg/kg doses to achieve comparable exposures to older children (b) (4)

The to-be-marketed formulation of benznidazole was not used in the clinical trials supporting this application. The formulation used in the de Andrade and Sosa Estani trials and the Viotti study was Radanil, a Roche product, which is no longer available. The applicant conducted two clinical pharmacology studies with the to-be-marketed formulation and provided a cross-study comparison of benznidazole exposure with the to-be-marketed 100 mg tablet with exposure reported in a study of Radanil pharmacokinetics (PK) published in 1979[9]. Estimates of $AUC_{0-\infty}$ and C_{max} were similar between the formulations. The applicant did not submit data comparing the to-be-marketed formulation with the LAFEPE product used in the Molina and DNDi trials.

The applicant proposed dosing of (b) (4) ased on pharmacometric analyses which included information from a population PK study of the Radanil formulation in children 2 to 12 years of age[10], the OCP review team recommended a weight-based dosing regimen of 5 to 8 mg/kg/day for children 2 to 12 years of age and provided the following dosing instruction table:

Table 1. Dosing Instructions

Body weight range (kg)	BID Dose (mg)*
<15	50
15-<20	62.5
20-<30	75
30-<40	100
40-<60	150
≥60	200

* Administered twice daily approximately 12 hours apart for 60 days
From FDA clinical pharmacology review

Complete ADME information is not available for benznidazole, and the OCP review team had no dosing recommendation for patients with renal or hepatic impairment.

[9] Raaflaub J, Ziegler WH. Single-dose pharmacokinetics of the trypanosomicide benznidazole in man. Arzmeimittel-Forschung/Drug Res 1979;29:1611-4.
[10] Altcheh J, Moscatelli G, Mastrantonio G, et al. Population pharmacokinetic study of benznidazole in pediatric Chagas disease suggests efficacy despite lower plasma concentrations than in adults. PLoS Negl Trop Dis 2014;8:e2907.

The applicant provided reports from in vitro studies that evaluated the role of hepatic enzymes and transporters in benznidazole disposition and drug interaction potential. Information on benznidazole disposition and excretion pathways in humans is not available. The applicant has agreed to conduct a mass balance/ADME study as a postmarketing requirement. Based on the results, additional studies may be needed.

Consultation from CDER's QT Interdisciplinary Review Team (QT-IRT) was obtained before the NDA was submitted. QT-IRT stated that the world-wide clinical use of benznidazole was persuasive, that the likelihood that benznidazole would significantly prolong the QT interval was low, and that a thorough QT study was not needed.

The OCP review team concluded that this application was approvable from a clinical pharmacology perspective provided that agreement was reached on postmarketing requirements and the dosing regimen. The OCP review team concluded that the exposure bridge between the to-be-marketed formulation and the Radanil product was adequate. No data were submitted comparing the to-be-marketed product with the LAFEPE product used in some of the clinical trials submitted by the applicant in this NDA. The OCP review team recommended different dosing from the applicant's proposal based on the available efficacy data in 6 to 12 year old children and pharmacokinetic data in 2 to 12 year old children in studies using the Radanil product. The OCP review team concluded that the applicant had not provided adequate efficacy and safety data to support the proposed dosing (b) (4) (b) (4).

6. Clinical Microbiology

Shukal Bala, Ph.D., was the clinical microbiology reviewer for this application. Consultation was also obtained from Noel Gerald, Ph.D., Kathleen Whitaker, Ph.D., and David Goodwin, Ph.D., of the Division of Microbiology Devices, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health (CDRH). Their findings and recommendations are summarized below.

Benznidazole is a nitroimidazole that inhibits the synthesis of DNA, RNA, and proteins within *T. cruzi*. The precise mechanism of action is unknown. Benznidazole is active against *T. cruzi* trypomastigotes, amastigotes, and epimastigotes. The sensitivity to benznidazole of *T. cruzi* strains from different geographic regions may vary.

In vitro activity of benznidazole has been evaluated against epimastigotes and amastigotes of strains of *T. cruzi* belonging to different distinct typing units. The methods used in these studies varied. Time-kill studies suggest that the activity of benznidazole is concentration- and time-dependent. The clinical relevance of in vitro sensitivity testing is unknown.

The activity of benznidazole has been evaluated in mice, rabbits, and dogs infected with *T. cruzi*. Findings vary with the experimental conditions, including parasite strain. Benznidazole decreased parasite load in blood and tissues, improved survival, and decreased the antibody response to *T. cruzi* antigens in murine models of acute infection. Treatment during the chronic phase of infection decreased the development of cardiomyopathy but did not eradicate

parasites. In rabbits, benznidazole reduced the duration of parasitemia during the acute phase of infection, but myocarditis developed in both treated and untreated rabbits, and there was no effect on survival. There was no effect of treatment on antibody response. Lymphomas developed in all groups, including uninfected rabbits treated with benznidazole. In dogs, benznidazole administered during the acute phase reduced parasitemia. Both treated and untreated dogs survived the period of observation. Antibody titers in treated dogs were lower than those in untreated dogs. Antibody responses varied depending on the infecting strain. Treatment of dogs in the chronic phase of infection did not prevent the development of cardiomyopathy. Epimastigote ELISA antibody responses were reduced in treated dogs, but trypomastigote ELISA responses were unchanged.

In vitro and mouse studies suggest a potential for development of resistance to benznidazole. The mechanisms of resistance appear to be multifactorial, including decreased activity due to a mutation in the nitroreductase gene, higher efflux activity due to overexpression of genes that encode p-glycoprotein and genes that encode ATP-binding cassette transporters, and overexpression of other genes that may enable parasite survival. The clinical relevance of these findings is unknown.

The de Andrade and Sosa Estani studies submitted in support of this application relied on serologic methods for the diagnosis of Chagas disease and to evaluate the response to therapy. The serologic tests included conventional assays (IHA, IFA, ELISA) that used antigens from whole cell lysates from cultured parasites or whole cultured parasites on slides and nonconventional assays (F29 ELISA and AT ELISA) that used recombinant F29 antigen or purified F2/3 antigens from cultured trypomastigotes. The nonconventional assays may reflect the antibody response to live parasites. These studies demonstrated that benznidazole treatment decreased the proportion of patients who remain seropositive using the F29 and AT ELISA assays and suggested that treatment reduced antibody titers measured by the conventional assays. The serologic tests used in these studies were not FDA-cleared.

The CDRH reviewers addressed the validation of the serologic tests that were used in these studies. They highlighted the uncertainty about the performance characteristics of the assays and the ability of the results to predict ultimate clinical benefit. Regarding the ELISA assays, they noted that changes in numerical results (optical densities or signal-to-cutoff indices) should not be used for quantitative assessment of antibody decreases and that qualitative results (positive or negative) were more appropriate interpretations for these single-read ELISAs. Quantitative assays would require additional supporting documentation. There were no data on the precision of the assays, the use of calibrators was not always clear, and the studies were performed before the issuance of WHO International Reference Standards for antibodies to *T. cruzi*. The nonconventional assays used may be less sensitive, may miss important subpopulations of antibody signal, and may be more susceptible to regional differences in circulating parasite strains, which could produce false-negative results and overestimate drug performance. It is unclear how well negative results with nonconventional assays will predict ultimate clinical benefit. The CDRH reviewers recommended relying on clinical outcome measures as primary endpoints.

The Viotti study of long-term outcomes in adults used serologic methods alone for diagnosis. The applicant stated that these were performed in the same laboratory using the same methods as those used for the Sosa Estani study.

The Molina study of posaconazole vs. benznidazole and the DNDi study of ravuconazole vs. benznidazole vs. placebo used serology and real-time PCR (RT-PCR) for patient enrollment and based the efficacy assessments on RT-PCR. Follow-up was for a period of one year only. Dr. Bala noted that all patients remained seropositive by conventional serology. Benznidazole-treated patients were more likely to become RT-PCR-negative than placebo-treated patients. The active therapies cleared parasitemia as measured by RT-PCR in a high proportion of patients by the end of therapy. Some patients were only transiently PCR-negative; RT-PCR reverted to positive in most patients treated with posaconazole or ravuconazole, but also in some patients treated with benznidazole. It is unclear if this was due to intermittent release of DNA, indicating treatment failure, or to limitations of the assay. Information supporting the validation of the RT-PCR assay was inadequate. A negative result may be indicative only of the absence of circulating DNA; the clinical relevance of a negative result is unknown.

A more detailed discussion of the study results is presented in the next section.

Dr. Bala concluded that the studies suggest that benznidazole treatment decreases antibody titers against *T. cruzi*, decreases the number of patients who remain seropositive, especially with the nonconventional F29 and AT ELISA assays, and decreases the risk of disease progression. This application was approvable from a clinical microbiology perspective pending agreement on labeling. She recommended that a postmarketing study be conducted in asymptomatic patients, including children, to confirm the findings of the nonconventional assays and to evaluate the performance of the serologic assays. The CDRH reviewers' concerns about validation of the serologic tests can be addressed in a required postmarketing study (b) (4)

7. Clinical/Statistical- Efficacy

Maria Allende, M.D., was the clinical reviewer, and Felicia Griffin, Ph.D., and Janelle Charles, Ph.D., were the statistical reviewers for this application. The applicant submitted patient-level data from four published and one unpublished controlled clinical studies:

1. de Andrade ALSS, Zicker F, de Oliveria RM, et al. Randomised trial of benznidazole in treatment of early *Trypanosoma cruzi* infection. Lancet 1996;348:1407-13.
2. Sosa Estani S, Segura EL, Ruiz AM, et al. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. Am J Trop Med Hyg 1998;59:526-9.
3. Viotti R, Vigliano C, Lococo B, et al. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment. Ann Intern Med 2006;144:724-34.
4. Molina I, Gomez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. New Engl J Med 2014;370:1899-908.

5. A clinical study report from a phase 2 trial (DNDi-CH-E1224-001) sponsored by the Drugs for Neglected Diseases Initiative (DNDi) of E1224 (fosravuconazole, a prodrug of ravuconazole) vs. benznidazole vs. placebo for the treatment of adult patients with chronic indeterminate Chagas disease.

These studies were not conducted under an IND. For the de Andrade, Sosa Estani, and Viotti studies, no protocol or clinical study reports were submitted. For the Molina study, a copy of the protocol but no clinical study report was submitted. The patient-level data that were submitted were important for evaluating the outcomes of the studies, but the quantity and quality of the data were suboptimal, and additional information was generally unavailable.

de Andrade

This was a randomized, double blind trial of benznidazole, 7.5 mg/kg/d in two doses for 60 days, vs. placebo in the treatment of patients 7 to 12 years of age with early chronic *T. cruzi* infection. This study was conducted from 1991 to 1995 in an endemic area in Brazil. Asymptomatic children who were seropositive by four tests (IFA, IHA, conventional ELISA, and AT ELISA) were randomly assigned to receive either benznidazole or placebo. Randomization was stratified by school, age group, and sex in blocks of 6. Benznidazole 100 mg tablets (Roche) were reformulated into 50 mg tablets for administration to children. Patients were examined at 7, 14, and 45 days of treatment, and serum samples were obtained at baseline, day 60, and 3, 6, 12, and 36 months after completion of treatment. The primary endpoint was the absence of specific antibodies at the end of the three-year follow-up period. The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized patients who received at least one week of treatment.

A total of 130 patients were randomized, 65 to each arm. One benznidazole patient moved shortly after randomization and was excluded from all analyses. Demographic and baseline characteristics were similar between groups. Serologic results at 3 years were available for 112 patients (87%), 58 in the benznidazole group and 54 in the placebo group.

Table 2 shows the rates of seroconversion to negative for each assay at 36 months following completion of treatment. Missing values were imputed as positive. There was no control for type I error. There was a significant difference between groups in the percentage of patients who became seronegative by AT ELISA (ELISA index <1) and IHA. The publication states that 37 patients became seronegative by AT ELISA, but the data submitted in the NDA indicate that the correct number is 35. No patients became seronegative with all four assays.

Table 2: Seroconversion to negative at 36 months (ITT population)

	Benznidazole (N=64)		**Placebo (N=65)**		
Assay	**n**	**(%)**	**n**	**(%)**	**Difference (95% CI)**
AT ELISA	35	(54.7)	3	(4.6)	50.1 (35.8, 63.4)
Conventional ELISA	4	(6.3)	0	(0)	6.3 (0.3, 15.2)
IFA	3	(4.7)	0	(0)	4.7 (-1.0, 13.1)
IHA	9	(14.1)	0	(0)	14.1 (6.4, 25.0)

* Calculated using exact methods
Adapted from FDA statistical review, Tables 23, 25, 27, and 29

IFA and IHA titers and conventional ELISA index values were more likely to decline in patients treated with benznidazole. The clinical significance of seroreduction is less clear than that of seroconversion to negative, however.

The publication's authors stated that there was one case of complete right bundle branch block, a potential early sign of Chagas cardiomyopathy, which developed over the three-year follow-up period in the benznidazole group and four cases in the placebo group. This difference was not statistically significant.

In a subsequent publication[11], the authors reported AT ELISA findings from an additional three years of follow-up in this study cohort. In the ITT analysis, at the six-year follow-up, 47 of 64 (73.4%) patients in the benznidazole group and 12 of 65 (18.5%) patients in the placebo group were reported to be seronegative. Findings with conventional assays were not reported. No additional electrocardiographic abnormalities were found. These data were not submitted in the NDA.

Sosa Estani

This was a randomized, double blind trial of benznidazole, 5 mg/kg/d in two doses for 60 days, vs. placebo in the treatment of patients 6 to 12 years of age with indeterminate phase Chagas disease. This study was conducted from 1991 to 1995 in an endemic area in Argentina. Asymptomatic children with *T. cruzi* infection were randomly assigned to receive benznidazole (Radanil®, Roche) or placebo; the publication does not provide the serologic criteria for diagnosis, but a separate statistical analysis plan prepared by the applicant states that patients had at least two positive serologic tests (conventional ELISA, IHA, IFA). The randomization method was also not provided. Patients in each locality were matched by age; it is unclear if this means stratified. The publication states that "Continuous medical assistance (anamnesis, physical examinations, and electrocardiograms [ECGs]) was provided during the trial." Laboratory tests were obtained at days 21 and 60 of treatment, and serum samples were obtained at baseline, and at 3, 6, 12, 18, 24, and 48 months after initiation of treatment. In addition to conventional serologic tests, F29 ELISA testing was performed. The publication does not specifically state a primary endpoint; the statistical analysis plan submitted by the applicant states that the primary endpoint was the proportion of children seronegative by conventional ELISA at the four-year follow-up. The FDA analysis evaluated all serologic tests and used a modified ITT analysis of patients who were positive for a specific serologic test at baseline.

A total of 106 patients were randomized, 55 to benznidazole and 51 to placebo. Demographic and baseline characteristics were similar between groups; two children 14 years of age were enrolled.

[11] de Andrade ALSS, Martelli CMT, Oliveira RM, et al. Short report: benznidazole efficacy among *Trypanosoma cruzi*-infected adolescents after a six-year follow-up. Am J Trop Med Hyg 2004;71:594-7.

The publication states that 62% of benznidazole patients and no placebo patients became seronegative by F29 ELISA at the four-year follow-up. The FDA reviewers were unable to reproduce these results from the data submitted by the applicant. The results presented here are based on FDA analyses.

Table 3 shows the rates of seroconversion to negative for each assay at 48 months following completion of treatment. Missing values were imputed as positive. There was no control for type I error. There was a significant difference between groups in the percentage of patients who became seronegative by F29 ELISA. The differences in seroconversion rates for the conventional assays were not statistically significant. One patient became seronegative with all four assays.

Table 3: Seroconversion to negative at 48 months (Modified ITT population)

	Benznidazole		**Placebo**		
Assay	**n/N[a]**	**(%)**	**n/N[a]**	**(%)**	**Difference (95% CI)***
F29 ELISA	24/40	(60)	5/37	(13.5)	46.5 (24.5, 64.4)
Conventional ELISA	4/53	(7.5)	2/50	(4)	3.5 (-7.0, 14.9)
IFA	3/53	(5.7)	0/48	(0)	5.7 (-2.0, 16.0)
IHA	5/52	(9.6)	0/50	(0)	9.6 (1.6, 21.0)

[a] n/N = number with seroconversion to negative/number positive at baseline
* Calculated using exact methods
Adapted from FDA statistical review, Tables 5, 9, 13, and 17

IFA and IHA titers and conventional ELISA optical densities were more likely to decline in patients treated with benznidazole. As noted with the de Andrade study, the clinical significance of seroreduction is less clear than that of seroconversion to negative.

The publication's authors stated that no patients had clinical manifestations of Chagas disease during follow-up.

Viotti

This was a non-randomized, unblinded observational study comparing long-term outcomes in patients with chronic Chagas disease treated with benznidazole with outcomes in patients receiving no treatment. This study included patients who were evaluated at a Chagas disease center in Argentina between 1984 and 2001; follow-up ended in 2004. Patients 30 to 50 years of age with three positive serologic test results by complement fixation, IHA, IFA, or conventional ELISA and with no clinical signs of heart failure were eligible for enrollment. Potential patients were stratified by Kuschnir classification: group 0, positive serology, normal electrocardiogram (ECG) and chest x-ray, and no cardiac enlargement; group I, positive serology, abnormal ECG, normal chest x-ray, and no cardiac enlargement; group II, positive serology, abnormal ECG, chest x-ray with cardiac enlargement but no clinical signs of heart failure; and group III, positive serology, abnormal ECG, chest x-ray with cardiac enlargement, and clinical signs of heart failure. Only patients in Kuschnir groups 0, I, and II at baseline were eligible for enrollment. Patients with previous treatment for *T. cruzi* infection or with a variety of concomitant disorders were excluded. Eligible patients were assigned to receive either benznidazole, 5 mg/kg/d in two doses for 30 days, or no treatment. Treatment assignment was by an alternating sequence of treatment and control. If a patient withdrew from the study or

declined to participate, the next eligible patient was assigned to that respective group. Clinical status was evaluated at follow-up visits every 6, 4, and 3 months for patients in Kuschnir groups 0, I, and II, respectively. The primary outcome of the study was disease progression, defined as a change to a more advanced Kuschnir group or death. The primary analysis population was the ITT population of all patients assigned to treated and untreated groups. The planned sample size was 319 patients per group, based on the results of a previous study in which 17% of untreated patients had a change of clinical group over an 8-year period. The study was to be stopped when the sample size was reached or when a statistically significant difference in the primary outcome was attained. No adjustments were made for multiple testing.

A total of 598 patients were enrolled in the study and assigned to treatment; 32 patients withdrew, 11 who had been assigned to benznidazole and 21 who had been assigned to no treatment. The study population was 566 patients, with 283 patients in each group. The mean age of participants was 39.4 years; at baseline, 64% were in Kuschnir group 0, 26% in group I, and 10% in group II. Median time of follow-up was 10 years. Approximately 20% of patients in each group were lost to follow-up.

Table 4 shows the baseline Kuschnir groups along with changes in Kuschnir group or cardiac death for each arm. Overall, 12 of 283 (4.2%) patients in the benznidazole group changed Kuschnir group compared with 41 of 283 (14.5%) patients in the untreated group (difference -10.3%, 95% confidence interval (-15.2, -5.3)). For each Kuschnir group at baseline, treated patients were less likely than untreated patients to change clinical group. Three patients in the benznidazole group and 12 patients in the untreated group died during the follow-up period; the authors report that this difference was not significant when mortality data were adjusted for left ventricular ejection fraction.

Table 4: Change in Kuschnir group or cardiac death

Benznidazole	**New Kuschnir Group**			
Baseline Kuschnir Group	I	II	III	Death
0 (n=180)	5 (2.8%)	1 (0.6%)	0	0
I (n=73)		2 (2.7%)	0	1 (1.4%)
II (n=30)			1 (3.3%)	2 (6.7%)
Untreated	**New Kuschnir Group**			
Baseline Kuschnir Group	I	II	III	Death
0 (n=180)	11 (6.1%)	2 (1.1%)	0	0
I (n=75)		7 (9.3%)	3 (4.0%)	4 (5.3%)
II (n=28)			6 (21.1%)	8 (28.6%)

Adapted from FDA statistical review, Table 34

Conversion of serology to negative on three serologic tests was reported in 32 patients treated with benznidazole and in 12 untreated patients. Change in Kuschnir group was more frequent in patients with three persistently positive conventional serologic tests, and no patients who seroconverted to negative on conventional serologic tests changed Kuschnir group. Specific test results were not provided to FDA for review.

This study has a number of shortcomings. It was not randomized; treatment assignment was by an alternating sequence. It was unblinded. It is unclear whether the replacement of patients

who withdrew from the study led to a biased sample. No adjustments for multiple testing were planned or conducted, which could lead to erroneous claims of effectiveness. Approximately 20% of patients were lost to follow-up. Times to clinical events were not provided.

Molina

This was a randomized, open-label trial of posaconazole, 100 mg twice daily or 400 mg twice daily for 60 days, vs. benznidazole, 150 mg twice daily for 60 days, in the treatment of adult patients with chronic Chagas disease. This study was conducted from 2010 to 2013 in Spain. Patients with two positive serologic tests and a positive RT-PCR test were assigned 1:1:1 to receive posaconazole (low or high dose) or benznidazole (LAFEPE) and followed for one year. The primary endpoint was consistent PCR negativity over the post-treatment follow-up period. A total of 79 patients were randomized; one patient was withdrawn because of a randomization error. During treatment, all patients were negative for *T. cruzi* DNA by PCR after day 14, except for two patients in the posaconazole group on day 60. In the ITT analysis, during the follow-up period, 92% of patients in the low-dose posaconazole group, 81% of patients in the high-dose posaconazole group, and 38% of patients in the benznidazole group were positive for *T. cruzi* DNA by PCR. There were no significant differences in serologic tests. While the PCR findings suggest that benznidazole has greater activity against *T. cruzi* than posaconazole, the short follow-up period and use of a different formulation of benznidazole which cannot be bridged to the Chemo product limit the trial's usefulness.

DNDi

This was a randomized, evaluator-blind trial of three doses of E1224 (fosravuconazole) vs. benznidazole vs. placebo in the treatment of adult patients with chronic indeterminate Chagas disease. The study was conducted from 2011 to 2013 in Bolivia. Patients with two positive serologic tests and a positive PCR test were assigned to receive one of three doses of E1224 (high dose, low dose or short dose), benznidazole (LAFEPE), or placebo and followed for one year. The primary endpoint was parasitologic response as assessed by PCR at day 65. A total of 231 patients were randomized, with 45 to 48 in each of the five groups. In the ITT analysis at day 65, PCR was negative in at least 76% of patients receiving active treatment as compared with 26% of patients receiving placebo. At one year, PCR was negative in 9% of placebo recipients, between 8% and 29% of E1224 recipients, and 82% of benznidazole recipients. As with the Molina study, the PCR findings suggest that benznidazole has greater activity against *T. cruzi* than E1224 or placebo, but the short follow-up period and use of a different formulation of benznidazole which cannot be bridged to the Chemo product limit this trial's usefulness.

Conclusions

In her review, Dr. Allende recommended that benznidazole be approved for treatment of acute and chronic indeterminate Chagas disease without established cardiomyopathy. She considered findings from several prospective, non-randomized observational studies to support the findings from the Viotti study in formulating her recommendation to treat adults with chronic indeterminate disease. She also cited several additional studies to support a

recommendation to approve benznidazole for the treatment of congenital and acute Chagas disease. She noted, however, that pharmacokinetic data are lacking in children under 2 years of age and that a dose cannot be recommended.

Dr. Griffin recommended that the results of the de Andrade and Sosa Estani trials be considered adequate evidence of efficacy to support approval of benznidazole for treatment of Chagas disease in children. She stated that the Viotti study, along with the Molina and DNDi studies, provides some support of the effectiveness of benznidazole in the adult population.

We concur that the applicant has presented substantial evidence from adequate and well-controlled trials to support a Subpart H approval of benznidazole for the treatment of Chagas disease in children. The de Andrade and Sosa Estani trials demonstrated an effect on a surrogate endpoint, conversion to negative with nonconventional serologic assays, that is reasonably likely to predict clinical benefit. Conversion to negative with nonconventional assays occurred more rapidly in these trials than with conventional assays. These studies were performed in children 6 to 12 years of age. Efficacy in children 2 to 5 years of age can be extrapolated from the data from older children. The course of Chagas disease and the effect of the drug are sufficiently similar in these populations, and the applicant has presented information to support dosing and an acceptable safety profile for the younger age group. Subpart H approval carries a requirement to study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit. The clinical endpoint of interest in the pediatric population is seroconversion to negative using conventional serologic tests. In addition to the Viotti study described above, there are a number of published observational studies[12,13] that provide evidence that seroconversion to negative using conventional serologic tests is associated with a lower risk of development of cardiac abnormalities in adults. Prevention of development of cardiomyopathy would take decades to demonstrate and is clearly a difficult trial endpoint for the pediatric population. The required confirmatory study will be an (b) (4) single-arm study (b) (4)

(b) (4)

[12] Viotti R, Vigliano C, Armenti H, Segura E. Treatment of chronic Chagas disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up. Am Heart J 1994;127:151-62.
[13] Fabbro D, Streiger ML, Arias ED, et al.Trypanocide treatment among adults with chronic Chagas disease living in Santa Fe City (Argentina), over a mean follow-up of 21 years: parasitological, serological and clinical evolution. Revista da Sociedade Brasileira de Medicina Tropical 2007; 40: 1-10.

(b) (4)

The additional supportive evidence cited by Dr. Allende in her review consists largely of observational studies that have potential biases. A recent Cochrane review of drugs for chronic asymptomatic *T. cruzi* infection[14] included the Viotti study and many other observational studies and concluded that data regarding outcomes important to patients were inconsistent and of low quality; effect size estimates were imprecise and statistically heterogeneous. The authors stated that methodologically robust studies were needed to provide convincing results before therapy can be recommended in general for chronically infected patients.

There is a lack of randomized, controlled trials that successfully demonstrate either seroconversion to negative or other clinical benefit in adults. The BENEFIT trial[15] was a randomized, double-blind trial of benznidazole vs. placebo in adult patients with Chagas cardiomyopathy. Patients with at least two positive serologic tests and evidence of cardiomyopathy based on ECG findings, increased cardiothoracic ratio, complex ventricular arrhythmias, or echocardiographic changes were randomized to receive benznidazole (Roche or LAFEPE) or placebo and followed for a mean of 5.4 years. The primary endpoint was the first occurrence of death, resuscitated cardiac arrest, insertion of a pacemaker or implantable cardioverter-defibrillator, sustained ventricular tachycardia, cardiac transplantation, new heart failure, stroke or transient ischemic attack, or a systemic or pulmonary thromboembolic event. A total of 2854 patients from 49 centers in 5 countries in Central and South America were randomized. The mean age of patients was 55 years, and 97% had New York Heart Association class I or II heart failure. There were no significant differences between groups in the time-to-event analysis. The primary outcome occurred in 27.5% of patients in the benznidazole group and in 29.1% of the placebo group. There were also no differences between groups in any of the primary outcome components. Treatment of patients with established Chagas cardiomyopathy with benznidazole did not reduce cardiac disease progression through 5 years of follow-up. Based on inclusion and exclusion criteria, some of the patients enrolled in the Viotti study would have been eligible to enroll in the BENEFIT Trial (e.g., patients classified as Kuschnir groups I or II). The overlap of inclusion and exclusion criteria between the Viotti study and the failed BENEFIT Trial underscores the need for an additional adequate and well-controlled trial in adults. This trial should enroll adult patients with chronic indeterminate Chagas disease without evidence of cardiac abnormalities.

(b) (4)

[14] Villar JC, Perez JG, Cortes OL, et al. Trypanocidal drugs for chronic asymptomatic *Trypanosoma cruzi* infection. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD003463. DOI: 10.1002/14651858.CD003463.pub2.

[15] Morillo CA, Marin-Neto JA, Avezum A, et al. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. New Engl J Med 2015;373:1295-306.

(b) (4)

[redacted]

8. Safety

Maria Allende, M.D., performed the safety review for this application.

The safety information from the studies for which the applicant had patient-level data is summarized below.

de Andrade

An adverse event listing was submitted. Seven of 64 patients receiving benznidazole and 2 of 65 patients receiving placebo had skin lesions reported. No other information was provided. The publication states that nausea, anorexia, headache, stomach ache, and arthralgia were reported by fewer than 5% of patients. Rash and pruritus were more common with benznidazole and resulted in one withdrawal from the study. The frequency of anemia was stated to be similar between groups, and no patients developed leukopenia or neutropenia. Transaminases, blood urea nitrogen, and creatinine did not change significantly.

Sosa Estani

An adverse event listing was submitted. The most frequently reported adverse reactions in patients treated with benznidazole were abdominal pain (25%), rash (16%), decreased weight (13%), and headache (7%). No other information was provided. The publication states that the adverse reactions resolved when treatment was stopped, and that clinical laboratory examinations did not differ between groups.

Altcheh

Adverse event listings were provided for the population PK study of 39 children 2 to 12 years of age who received 5 to 8 mg/kg of benznidazole for 60 days. No serious adverse events were reported. Two patients discontinued treatment because of rash which reappeared with drug reintroduction. Additional adverse events included eosinophilia, urticaria, leukopenia, neutropenia, abdominal pain, and loss of appetite.

Viotti

Adverse event listings simply stated whether a patient had an adverse event; no specific terms were provided. The publication states that benznidazole was discontinued in 37 of 283 patients (13%), 33 discontinuations were because of severe allergic dermatitis and 4 were because of gastrointestinal disorders. Additional adverse reactions included headache and pruritus.

Molina

Adverse event listings were provided for this trial which used the LAFEPE formulation of benznidazole as an active control; 26 patients received benznidazole. Five patients discontinued benznidazole because of severe allergic dermatitis. The most common adverse events reported in patients receiving benznidazole were cutaneous reactions, headache, and gastrointestinal symptoms. Increased alkaline phosphatase was the most commonly reported laboratory test abnormality.

DNDi

Adverse event listings were provided for this trial which used the LAFEPE formulation of benznidazole as an active control; 45 patients received benznidazole. Two patients had serious adverse events (anembryonic pregnancy and acute bronchitis) and 4 patients discontinued treatment because of adverse events (all hypersensitivity, 1 with concomitant ALT elevation). The most common adverse events reported in patients receiving benznidazole were headache, hypersensitivity, nausea, neutropenia, and pruritus.

Dr. Allende also performed an extensive literature review for additional information to include in labeling. The most frequently reported adverse events are cutaneous reactions, which are usually mild but which may be severe and require discontinuation of therapy. Peripheral neuropathy and paresthesia are also frequently reported. Bone marrow depression has also been reported. Benznidazole seems to be tolerated better in children than in adults.

Benznidazole, a nitroimidazole, is contraindicated in patients who have taken disulfiram within the preceding two weeks. Consumption of alcohol or products containing propylene glycol may produce a disulfiram-like reaction in patients taking benznidazole.

The Warnings and Precautions section of the label includes information about the potential for genotoxicity and carcinogenicity, embryofetal toxicity, hypersensitivity skin reactions, central and peripheral nervous system effects, and hematologic effects.

9. Advisory Committee Meeting

An advisory committee was not convened because there were no issues raised in the course of the NDA review that would benefit from advisory committee discussion.

10. Pediatrics

The applicant has presented substantial evidence from adequate and well-controlled trials to support a Subpart H approval of benznidazole for the treatment of Chagas disease in children. The de Andrade and Sosa Estani trials demonstrated an effect on a surrogate endpoint, conversion to negative with nonconventional serologic assays, that is reasonably likely to predict clinical benefit. These trials were performed in children 6 to 12 years of age. Efficacy in children 2 to 5 years of age can be extrapolated from the data from older children. The course of Chagas disease and the effect of the drug are sufficiently similar in these populations, and the applicant has presented information to support dosing and an acceptable safety profile for the younger age group. Subpart H approval carries a requirement to study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit. The clinical benefit of interest in the pediatric population is seroconversion to negative using conventional serologic tests. The required confirmatory study will be a (b) (4) single-arm study (b) (4)

Chemo was granted orphan drug designation for benznidazole for the treatment of Chagas disease on April 14, 2014. There is no requirement to perform studies in other pediatric age groups. There is also no requirement for review by the Pediatric Review Committee.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspected Chemo Research to review standard operating procedures, the handling of datasets, and the creation of data tabulations. The Sosa Estani clinical site was also reviewed. No important deficiencies were identified, and no Form FDA 483, Inspectional Observations, was issued. The OSI reviewer, John Lee, M.D., concluded that the data from the published studies appear reliable as reported in the NDA.

The Office of Study Integrity and Surveillance (OSIS) inspected the clinical site for the bioavailability studies and found the data to be reliable. This conclusion was based on a summary of the inspection findings provided by the Office of Regulatory Affairs investigator.

12. Labeling

A proprietary name has not been determined.

Recommendations from the Office of Prescription Drug Promotion, the Division of Medical Policy Programs, the Division of Medication Error Prevention and Analysis, and the Division of Pediatric and Maternal Health were incorporated into labeling.

13. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The applicant has agreed to the following accelerated approval PMR:

PMR 3247-1: Conduct a prospective, single-arm, multicenter trial, with historical controls, to evaluate safety, efficacy and pharmacokinetics of benznidazole tablets for treatment of Chagas disease in children.

Draft protocol submission:	11/2017
Final protocol submission:	03/2018
Interim pharmacokinetics report:	12/2018
Interim trial report:	12/2021
Trial completion:	12/2025
Final report submission:	05/2026

The applicant has agreed to the following additional PMRs:

PMR 3247-2: Conduct a human absorption, distribution, metabolism, and excretion (ADME)/mass balance study to evaluate the routes and rates of benznidazole excretion, ascertain whether benznidazole has circulating drug metabolites, and if identified, evaluate the routes and rates of excretion for benznidazole metabolites.

Draft protocol submission:	10/2017
Final protocol Submission:	11/2017
Study completion:	04/2018
Final report submission:	08/2018

PMR 3247-3: Study AB21206 entitled Benznidazole - Fertility toxicity study by the oral route (twice daily gavage) in the male rat (Segment I) followed by a 13-week treatment-free period.

Final protocol submission:	Submitted
Study completion:	Completed
Final report submission:	09/2017

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/s/

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08/29/2017

SUMATHI NAMBIAR
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