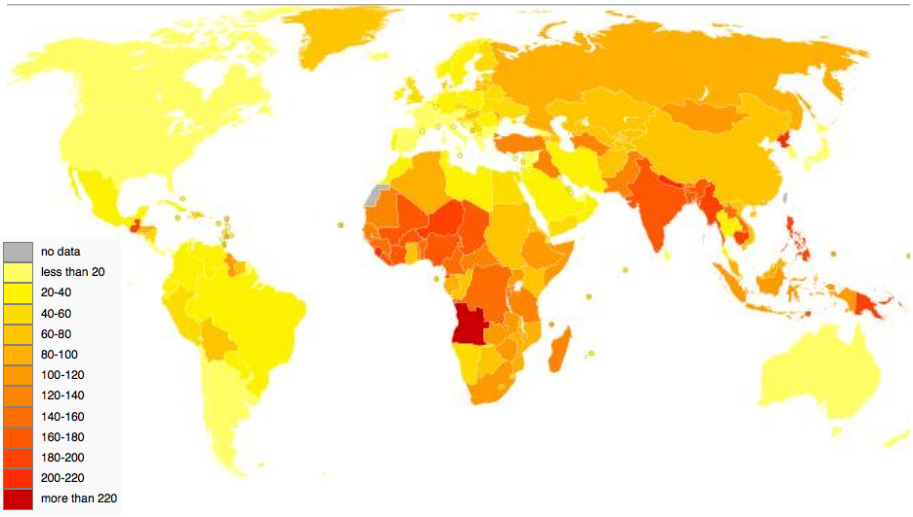
# SQ109 for the Treatment of *Helicobacter pylori* infection

***Clinical Development Status: Phase 2***

Since 2000, Sequella applied its scientific expertise in drug development to identify, characterize, and complete preclinical evaluation of SQ109, a promising drug candidate that was developed in partnership with the National Institutes of Health. SQ109 was discovered at Sequella based on activity against the causative bacterial agent of tuberculosis (TB)[1,2] and was safe and well-tolerated in three Phase 1 clinical trials. While clinical development of SQ109 for the treatment of TB continues, we recently discovered that SQ109 also has excellent activity against *H. pylori*. Its clinical-stage status for TB provided us with a unique opportunity to move immediately to a Phase 2 clinical trial for the treatment of *H. pylori* infection in 2012.

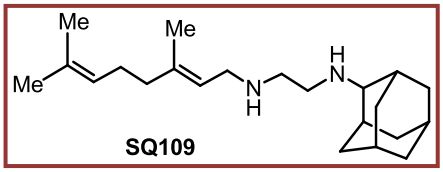
***H. pylori* infections lead to peptic ulcers and gastric cancer.** The global prevalence of *H. pylori* infection is estimated at 50%, and 10-20% of infected adults develop peptic ulcer disease. In the U.S. alone, there are 6 million people suffering from peptic ulcers treated with a combination of 3 antibiotics. In addition, *H. pylori* infection is associated with a significantly increased risk of gastric cancer, which kills more than 700,000 people each year. Treatments for gastric cancer are limited, and the 5-year survival rate in the U.S. is <15%. Eradication of *H. pylori* in infected individuals who do not yet have pre-malignant lesions significantly decreases the risk of developing cancer.

*Disability adjusted life year (DALY) rates from peptic ulcer disease by country (per 100,000 inhabitants).*



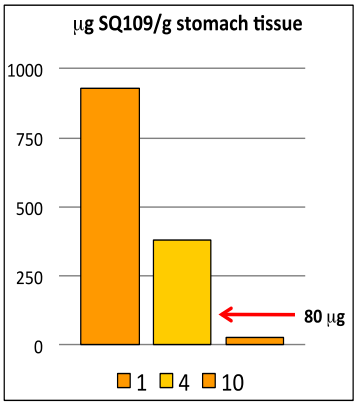

*H. pylori* is susceptible *in vitro* to several antibiotics, but there are no drugs that are effective *in vivo* when delivered as a monotherapy. Because *H. pylori* infection is recalcitrant to monotherapy, standard guidelines for treatment consist of 7 to 14 days of therapy with three drugs. Recent success rates of this regimen have decreased to 75% in some areas of the world, which is due at least partly to increasing drug resistance. As a result, new treatments with activity against drug-resistant *H. pylori* are urgently needed.

**Discovery of SQ109.** SQ109 was discovered by screening a combinatorial library to identify new drugs for TB, and represents an entirely new class of antibacterial compounds with a novel mechanism of action.[2] Interestingly, the *in vitro* bacterial mutation rate for SQ109 is very low, suggesting that development of resistance to the drug may be difficult to achieve. Later studies found that SQ109 also had activity against a limited set of additional bacteria and fungi.



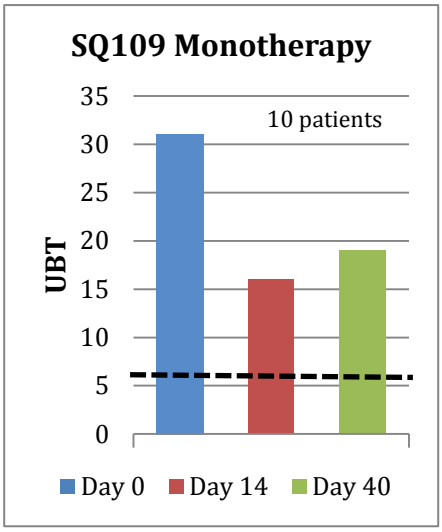
SQ109

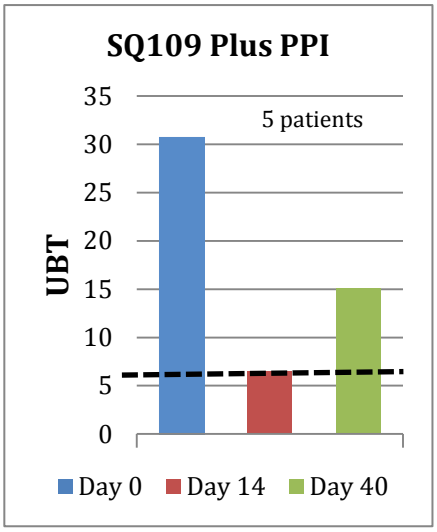
**SQ109 has very promising activity against *H. pylori.*** SQ109 is active against all strains of *H. pylori* tested, with an MIC of 8-20 µM.[3] It kills 99.99% of *H. pylori* within 4 hours at a concentration well below that maintained in stomach for this length of time after oral administration (see Figure). In addition, SQ109 demonstrated superior efficacy compared to amoxicillin and metronidazole, suggesting that incorporation of SQ109 into the multidrug regimen could have significant benefits over standard-of-care.




**Pharmacology**. Stomach concentration of SQ109, based on animal studies conducted with radioactive drug, is estimated at >300 µg/mL at 4 hr, at least 15-fold higher than the SQ109 *H. pylori* MIC and >4 times the concentration of drug that kills *H. pylori* in 4 hr.[4] In bactericidal time course studies, SQ109 demonstrated both thermal and pH stability, suggesting that it will be active in stomach tissues.[3]

**Clinical Development.** SQ109 is both safe and well-tolerated up to 300 mg daily (highest dose tested) for up to 14 days. SQ109 is currently in clinical development in an open-label clinical assessment of *H. pylori*-infected symptom-free individuals in the U.S. (IND# 110,346). The FDA-approved biomarker for *H. pylori* infection, urea breath test (UBT), was used to demonstrate drug activity. Two phases of this trial are complete, SQ109 monotherapy and SQ109 + a protein pump inhibitor (PPI, see Figures below). SQ109 showed a clear efficacy signal in infected patients: the combination of SQ109+PPI lowered the UBT to levels considered negative (black line). Similarly as other single antibiotics, *H. pylori* cure was transient. The third phase of the trial will include addition of a second antibiotic and will start in Q3 2013.




**Market for New *H. pylori* Drugs.** *H. pylori*-related infections are part of the $24 billion worldwide gastrointestinal treatment market. The estimated antibiotic market in the U.S. is $500M, with additional large markets in Japan, China, and Russia, countries where *H. pylori* incidence and gastric cancer are particularly high.

**Intellectual Property.** Sequella has 20 or more issued patents and additional patent filings, including a U.S. patent for compositions of matter and uses of diamine anti-infectives. These patents provide broad coverage for composition, methods and use claims for treatment of TB, *H. pylori* infection, systemic fungal agents, and other infectious pathogens. Sequella issued and pending patents are in the U.S., EU, Japan, EME, South Africa, China, Eurasia, and other key international markets.


**References.** Copies of all referenced papers are available upon request: please contact katherinesacksteder@sequella.com.

1. Lee RE, Protopopova M, Crooks E, Slayden RA, Terrot M, Barry CE, 3rd. Combinatorial lead optimization of [1,2]-diamines based on ethambutol as potential antituberculosis preclinical candidates. J Comb Chem 2003;5:172-87.
2. Protopopova M, Hanrahan C, Nikonenko B, et al. Identification of a new antitubercular drug candidate, SQ109, from a combinatorial library of 1,2-ethylenediamines. J Antimicrob Chemother 2005;56:968-74.
3. Mokobongo M, Einck L, Merrell D. *In Vitro* Characterization of the Anti-bacterial Activity of SQ109 against *Helicobacter pylori*. submitted 2013.
4. Jia L, Tomaszewski JE, Hanrahan C, et al. Pharmacodynamics and pharmacokinetics of SQ109, a new diamine-based antitubercular drug. Br J Pharmacol 2005;144:80-7.