

# Novel therapies for secretory diarrhea

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This study aims to assess the efficacy and potency of newly developed small molecule inhibitors of the GC-C signaling pathway and of the CFTR chloride channel in native human intestinal tissue.

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruiting
<b>Health condition type</b>	Gastrointestinal infections
<b>Study type</b>	Observational invasive

## Summary

### ID

NL-OMON39183

### Source

ToetsingOnline

### Brief title

Novel therapies for SD

### Condition

- Gastrointestinal infections
- Bacterial infectious disorders

### Synonym

ETEC infection, Traveler's diarrhea

### Research involving

Human

### Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam

**Source(s) of monetary or material Support:** Ministerie van OC&W, Institute for OneWorld Health; iOWH (NGO)

## Intervention

**Keyword:** ETEC, guanylyl cyclases, heat-stable toxin, secretory diarrhea

## Outcome measures

### Primary outcome

The effect of 6 GC-C signaling blockers and of 4 CFTR inhibitors on the pro-secretory response of human colon, assessed by ICM.

### Secondary outcome

The effect of 6 GC-C signaling blockers on GC-C-independent intestinal solute transport, assessed by ICM (off-target effects).

## Study description

### Background summary

Hyperactivation of the enzyme guanylyl cyclase C (GC-C) followed by excessive production of the signaling molecule cyclic GMP in the intestinal epithelium plays a central role in the disease mechanism of secretory diarrhea (SD) and, possibly, the irritable bowel syndrome (IBS-d). Newly developed inhibitors of GC-C signaling, shown to exert an anti-secretory and pro-absorptive effect on salt-and water transport in cultured enterocytes and in animal models, may therefore be used to treat SD. Activation of GC-C and of the enzyme adenylyl cyclase (AC) both result in the opening of CFTR, the major if not sole apical chloride channel in intestinal epithelium, encoded by the cystic fibrosis gene. Pharmacological inhibitors of CFTR are therefore expected to inhibit both GC-C and AC-mediated SD, including cholera, but such an inhibition has not yet been demonstrated convincingly in human intestine at the pre-clinical stage.

### Study objective

This study aims to assess the efficacy and potency of newly developed small molecule inhibitors of the GC-C signaling pathway and of the CFTR chloride channel in native human intestinal tissue.

### Study design

Rectal biopsies will be obtained from healthy volunteers. The effect of the

inhibitor compounds on the GC-C-and AC-mediated fluid secretory response of the intestinal mucosa will be studied ex vivo.

The test compounds have been selected on the basis of efficacy and potency in cell models of GC-C- and AC- mediated pro-secretory signaling. In view of subsequent structure-activity analysis, chemical diversity was also considered. The ex vivo testing is performed by the intestinal current measurement (ICM) technique in micro-Ussing chambers. These experiments will show whether the GC-C- and CFTR-antagonistic action of our current selection of compounds, established in cell and animal models, is retained in native human intestine. Thus, they will also affirm, or refute, the validity of our preceding selection procedure, and allow structure-activity analysis to aid further development of novel anti-diarrheal drugs.

## **Intervention**

Biopsies will be sampled from the rectum with a suction biopsy device.

## **Study burden and risks**

The procedure to obtain rectal biopsies can be completed within 15 minutes. Including anamnesis, the whole procedure will take about 30 min. Tissue sampling is virtually painless, although accompanied sporadically with the loss of minute quantities of blood. The procedure is regularly performed for screening and research purposes in the context of Hirschsprung\*s disease and cystic fibrosis. From this practice, it can be deduced that the risk of serious adverse effects is negligible.

No benefits are associated with participation.

## **Contacts**

### **Public**

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

Must be 18-55 years old.

Enrollment by informed written consent

### Exclusion criteria

Liver conditions; signs of portal hypertension

Coagulation disorders or use of anti-coagulants

(Chronic) constipation. (As this may indicate aberrant intestinal ion and fluid transport.)

## Study design

### Design

**Study type:** Observational invasive

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Treatment

### Recruitment

NL

Recruitment status: Recruiting

Start date (anticipated):	05-09-2013
Enrollment:	32
Type:	Actual

## Ethics review

Approved WMO	
Date:	16-04-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

Register	ID
CCMO	NL40609.078.12