S1. Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Male or female volunteers aged 18 – 49 years, inclusive
2. Able to give written informed consent
3. Healthy (no clinically significant health concerns), as determined by medical history, physical examination, 12-lead ECG, and vital signs at screening
4. Safety laboratory values within the following range criteria at screening:
   a. Laboratory normal range (< grade 1 elevation from normal) or decrease from normal with no clinical significance (NCS) for alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin,
   b. Laboratory normal range (< grade 1 decrease from normal) or elevated from normal with NCS for phosphorous (hypophosphatemia), neutrophils, and urine protein;
   c. Laboratory normal range (< grade 1 elevation or decrease) for white blood cells (WBC);
   d. Laboratory normal range or up to grade 1 abnormality with no NCS for:
      - decreased: albumin, magnesium, total protein, hemoglobin, lymphocytes and platelets;
      - elevated: amylase, BUN, CPK, creatinine and eosinophils;
      - elevated or decreased: calcium, glucose, potassium and sodium;
   e. Negative laboratory value or positive value with NCS for blood urine
5. Body mass index between 17 and 35 at screening
6. Comprehension of the study requirements with ability and willingness to complete all assessments and comply with scheduled visits and contacts
7. Female participants must have a negative pregnancy test at baseline and fulfill one of the following criteria:
   a. At least one year post-menopausal;
   b. Surgically sterile;
   c. Willing to use oral, implantable, transdermal or injectable contraceptives for 30 days prior to and until 60 days after vaccination;
      i. A reliable form of contraception must be approved by the Investigator (e.g., double barrier method, Depo-Provera, intrauterine device, Norplant, oral contraceptives, contraceptive patches, abstinence)

Exclusion Criteria:

1. Receipt of any investigational norovirus vaccine within two years prior to study vaccination
2. Administration of any investigational vaccine, drug or device within 8 weeks preceding vaccination, or planned use of the above stated during the study through the 12-month safety follow-up
3. Administration of any licensed vaccine within 30 days prior to vaccination
4. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including institution of new medical/surgical treatment or significant dose alteration for uncontrolled symptoms or drug toxicity within 3 months of screening and reconfirmed at baseline
5. Any one of the following ECG findings within 30 days prior to vaccination:

a. QTcF interval duration > 460 msec (male) or > 470 msec (female);
b. QRS interval greater than 120 msec;
c. PR interval greater than 220 msec;
d. Clinically significant ST-T wave changes or pathologic Q waves

6. Positive serology for HIV-1 or HIV-2, or HBsAg or HCV antibodies
7. Cancer, or treatment for cancer treatment, within past 3 years (excluding basal cell carcinoma or squamous cell carcinoma)
8. History of a hypersensitivity or allergic reaction to any component of the investigational vaccine or placebo, including but not limited to fish gelatin. Subjects with known fish allergies should be excluded.
9. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus
10. Administration of any medications or treatments that may adversely affect the immune system such as allergy injections, immune globulin, interferon, immunomodulators, cytotoxic drugs or other drugs known to be associated with significant major organ toxicity, or systemic corticosteroids (oral or injectable) during 3 months prior to vaccination. Inhaled and topical corticosteroids allowed
11. Presence of household members who have received the Ad4 or Ad7 vaccines within 2 months prior to vaccination
12. Presence of household members who are neonates, pregnant women, or hematopoietic stem cell transplant or solid organ transplant recipients
13. History of drug, alcohol or chemical abuse within 1 year prior to vaccination
14. Receipt of blood or blood products 6 months prior to vaccination or planned administration during the follow-up study period
15. Donation of blood or blood products within 4 weeks prior to vaccination or planned donation during the study period
16. Acute disease within 72 hours prior to vaccination defined as the presence of a moderate or severe illness with or without fever (as determined by the Investigator through medical history and physical examination). (Assessment may be repeated during screening period)
17. Presence of a fever $\geq 38^{o}C$ measured orally at baseline (Assessment may be repeated during screening period)
18. Stool sample with occult blood at screening
19. Positive urine drug screen for drugs of abuse at screening
20. Positive breath or urine alcohol test at screening or baseline
21. Consistent/habitual smoking within 2 months prior to vaccination
22. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives or abdominal pain
23. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic
24. History of irritable bowel disease or other inflammatory digestive or gastrointestinal condition that could affect the distribution / safety evaluation of an orally administered vaccine targeting the mucosa of the small intestine.
    Such conditions may include but are not limited to:
    a. Esophageal Motility Disorder
    b. Malignancy
    c. Malabsorption

d. Pancreaticobiliary disorders
e. Irritable bowel syndrome
f. Inflammatory Bowel Disease
g. Surgical Resection
h. GERD
i. Hiatal Hernia
j. Peptic Ulcer
(History of cholecystectomy is not exclusionary)

25. Any condition that resulted in the absence or removal of the spleen
26. History of any form of angioedema
27. Use of concomitant medications such as those listed below

a. Proton pump inhibitors
b. Over-the-counter probiotics
c. H2-blockers
d. Anti-seizure medications
e. Pain relief medications (chronic use)
f. Cardiovascular drugs
g. Imidazoles, Triazoles, and Thiozole antifungals
h. Thyroid medications
i. Antidiarrheals
j. Antibiotics (within 24 hours prior to vaccination)
k. Any condition that, in the opinion of the Investigator, might interfere with ability to assess the primary study objectives

S2. Supplemental Materials and Methods

Fecal Sample Collection:

Study subjects were given the following protocol for stool sample collection: *Put the cold pack from the fecal collection kit in the freezer until ready to bring the sample in. Collect the stool samples as fresh as possible, such as morning of the visit. Samples should not be collected more than 48 hours in advance (make sure to store at cold temperature, preferentially within 24 hours of collection). Samples should be kept cold until they are brought to the site. Never freeze the samples. Put on the disposable gloves provided and collect the stool sample by catching it in the sterile cup so it does not fall in the water. Use the plastic spoon (inside of the fecal collection tube) to collect the stool sample. Insert the plastic spoon into the tube. Repeat one more time with a new tube for two tubes total. Bring the insulated bag to the visit.*

Preparation of Stool Extracts:

A 200 mg aliquot of each stool sample (preserved at -70^{o}C) was placed in pre-weighed tubes containing ~1.5 g of 2.3 mm zirconium beads (Biospec, Bartlesville, OK) and 1 ml of extraction buffer [phosphate buffered saline (PBS, pH 7.4) containing 0.01% soybean trypsin inhibitor,

0.1% ethylenediaminetetraacetic acid, 0.5% phenylmethanesulfonyl fluoride solution and 0.05% Tween 20, all from Sigma, St. Louis, MO]. Samples were subjected to three 1-min cycles of intense shaking (from top to bottom) on a Mini-Beadbeater-8 tissue homogenizer (Biospec, Bartlesville, OK) with 2 minute incubations on ice between cycles. Following the bead beating, samples were centrifuged at 14,000 rpm for 30 minutes at 4˚C. The supernatant was collected, added to 10 µl of 1% bovine serum albumin containing 0.1% sodium azide (v/v) (Sigma) and stored at -80˚C until use.

Saliva Sample Collection:

Study sites were given the following protocol for saliva sample collection: *From the saliva collection tube, remove the swab and have the subject gently chew the swab for approximately 45 seconds. Return the saturated swab to the suspended insert and close firmly with the stopper. Centrifuge at 4°C for 2 minutes at 1,000 x g at 4°C to collect the saliva sample in the bottom of the tube. Store sample at -80°C ± 15°C immediately and keep frozen until shipment. If it takes longer than 30 minutes, keep samples on ice or at 4° C. The samples should be frozen within 90 minutes of collection.*

S3. Supplementary Table: Summary of Treatment-Emergent Adverse Events (Unsolicited)

Adverse Events*	Placebo N=20	Low Dose N=23	High Dose N=23	All Treated N=46
Total Number of Subjects Reporting At Least One TEAE	12 (60%)	11 (48%)	10 (44%)	21 (46%)
Total Number of TEAEs	23 (115%)	30 (130%)	30 (130%)	60 (130%)
Gastrointestinal disorders	6 (30%)	0 (0%)	3 (13%)	3 (7%)
Abdominal distension	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Abdominal pain lower	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Constipation	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Diarrhoea	1 (5%)	0 (0%)	1 (4%)	1 (2%)
Eructation	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Lip dry	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Lip pain	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Nausea	2 (10%)	0 (0%)	1 (4%)	1 (2%)
Toothache	1 (5%)	0 (0%)	1 (4%)	1 (2%)
Vomiting	0 (0%)	0 (0%)	1 (4%)	1 (2%)
General disorders and administration site conditions	0 (0%)	1 (4%)	2 (9%)	3 (7%)
Chills	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Feeling hot	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Oedema peripheral	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Pain	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Infections and infestations	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Conjunctivitis	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Investigations	2 (10%)	4 (17%)	0 (0%)	4 (9%)

Adverse Events*	Placebo N=20	Low Dose N=23	High Dose N=23	All Treated N=46
Amylase increased	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Blood creatine phosphokinase increased	2 (10%)	3 (13%)	0 (0%)	3 (7%)
Blood urea increased	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Lipase increased	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Metabolism and nutrition disorders	2 (10%)	1 (4%)	4 (17%)	5 (11%)
Hyperglycaemia	1 (5%)	1 (4%)	0 (0%)	1 (2%)
Hypoglycaemia	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Hypophosphataemia	1 (5%)	0 (0%)	2 (9%)	2 (4%)
Increased appetite	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Musculoskeletal and connective tissue disorders	1 (5%)	1 (4%)	2 (9%)	3 (7%)
Back pain	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Musculoskeletal pain	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Neck pain	1 (5%)	0 (0%)	1 (4%)	1 (2%)
Nervous system disorders	3 (15%)	4 (17%)	4 (17%)	8 (17%)
Dizziness	1 (5%)	1 (4%)	1 (4%)	2 (4%)
Headache	2 (10%)	2 (9%)	4 (17%)	6 (13%)
Hypoaesthesia	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Presyncope	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Tremor	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Renal and urinary disorders	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Haematuria	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Respiratory, thoracic and mediastinal disorders	2 (10%)	4 (17%)	3 (13%)	7 (15%)
Cough	0 (0%)	0 (0%)	1 (4%)	1 (2%)
Lower respiratory tract congestion	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Nasal congestion	0 (0%)	1 (4%)	2 (9%)	3 (7%)
Oropharyngeal pain	0 (0%)	1 (4%)	1 (4%)	2 (4%)
Paranasal sinus discomfort	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Productive cough	1 (5%)	2 (9%)	0 (0%)	2 (4%)
Rhinorrhoea	0 (0%)	3 (13%)	0 (0%)	3 (7%)
Sinus congestion	0 (0%)	2 (9%)	0 (0%)	2 (4%)
Sneezing	0 (0%)	2 (9%)	0 (0%)	2 (4%)
Throat irritation	1 (5%)	1 (4%)	0 (0%)	1 (2%)
Skin and subcutaneous tissue disorders	0 (0%)	1 (4%)	1 (4%)	2 (4%)
Ecchymosis	0 (0%)	1 (4%)	1 (4%)	2 (4%)

*Adverse events are classified according to MedDRA® Version 19.0
TEAE = treatment-emergent adverse event
N = Total number of subjects included in the summarization

S4. **Supplementary Figure:** Pre-existing immunity

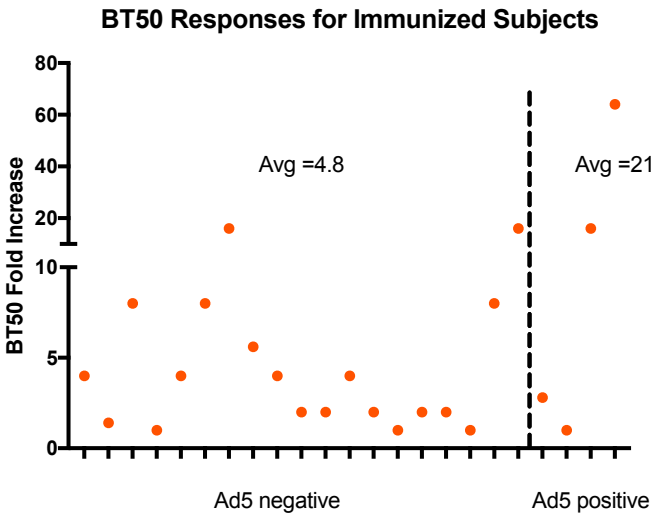

Figure S4. Anti-vector immunity does not affect the ability to elicit an immune response. Anti-vector immunity effects were explored by measuring the anti-vector titers at the day of dosing and determining whether pre-existing Ad5 titers had an effect on BT50. Subjects were divided into those with Ad5 titers ≥100 or < 100. From Figure S4, it is clear that Ad immunity does not change the vector's ability to elicit an increase in BT50 (P=0.46 by Mann-Whitney).

S5. Supplementary Figure: BT50 versus blood type

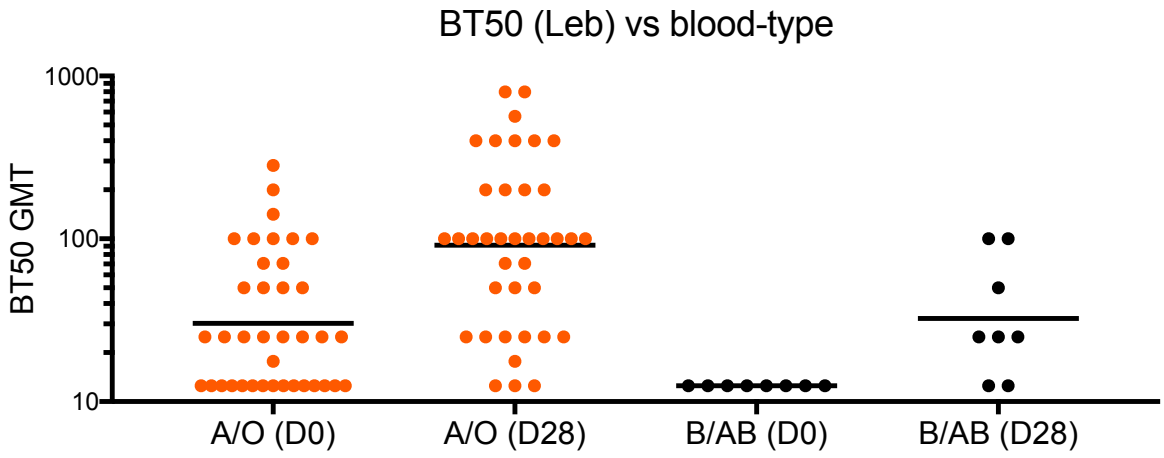

*Figure S5. BT50 titers versus blood type. Subjects with blood types A or O are more susceptible to GI.1 norovirus infection whereas subjects with blood types B or AB are more resistant to norovirus GI.1 infection (Hudson, et al., JID, **185**:1335, 2002). BT50 was examined pre- and post-immunization and divided by blood group for all immunized subjects. Consistent with the idea of blood type-based susceptibility, many subjects with A/O blood types had preexisting BT50 titers to GI.1 whereas the blood types B/AB had no measureable BT50 titers (a BT50 titer less than 25 is set to 12.5). Following immunization, several subjects in both groups had significant increases in BT50 titers. The A/O group started at a geometric mean titer of 30, rising to 91 after immunization and the B/AB group had a starting geometric mean of 12.5 rising to 32. In summary, all blood groups had the ability to respond to the vaccine, with some differences in starting titers likely related to prior infection exposure experience.*

S6. Supplementary Figure: Sample Table

Sample	Day 0	Day 7	Day 28	Day 180
PBMC	X	X	X	
Serum	X	X	X	X
Fecal	X		X	X