**Supplementary Information**

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‘Tissue distribution and abuse potential of prucalopride: findings from non-clinical and clinical studies’

*Drugs in Context*

**Table S1. Assay conditions for radioligand binding studies.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Receptor** | **Species** | **Receptor source** | **Assay conditions** | **Labelled ligand** | **Blank** | **Reference a** |
|  |  | **Cell line or tissue area, membrane preparation** | **Buffer, volume, temperature, time, filtration** | **Name,**  **concentration  (KD value)** | **Compound, concentration** |  |
| α1A-adrenergic | Human | CHO | F, pH 7.7, 0.5 mL,  37°C, 60 min, P | [3H]-Prazosin,  0.25 nM (0.15 nM) | Aceperone, 1 µM | Karliner *et al*. 19791 |
| α2A-adrenergic | Human | CHO | J, pH 7.6, 0.5 mL,  25°C, 30 min, T | [3H]-Rauwolscine,  1 nM (0.3 nM) | Oxymetazoline, 1 µM | Greenberg *et al*. 19762 |
| α2B-adrenergic | Human | CHO | J, pH 7.6, 0.5 mL,  25°C, 30 min, T | [3H]-Rauwolscine,  1 nM (0.63 nM) | Spiroxatrine, 1 µM |  |
| α2C-adrenergic | Human | CHO | J, pH 7.6, 0.5 mL,  25°C, 30 min, T | [3H]-Rauwolscine,  1 nM (0.10 nM) | Spiroxatrine, 1 µM |  |
| β1-adrenergic | Human | CHO | O, pH 7.4, 0.25 mL,  37°C, 60 min, T | [125I]-Iodocyanopindolol,  0.025 nM (0.009 nM) | Propranolol, 1 µM, | Luyten et al. 19913 |
| β2-adrenergic | Human | CHO | O, pH 7.4, 0.25 mL,  37°C, 60 min, T | [125I]-Iodocyanopindolol,  0.025 nM (0.004 nM) | Propranolol, 1 µM | Luyten et al. 19913 |
| β3-adrenergic | Human | CHO | O, pH 7.4, 0.25 mL,  37°C, 60 min, T | [125I]-Iodocyanopindolol,  0.20 nM (0.38 nM) | Bucindolol, 1 µM |  |
| Dopamine-D1 | Rat | Striatum, TP | C, pH 7.7, 0.5 mL,  37°C, 30 min, P | [3H]-SCH23390,  0.25 nM (0.46 nM) | Piflutixol, 1 µM | Schulz et al. 19844 |
| Dompamine-D2L | Human | CHO | C, pH 7.7, 0.5 mL,  37°C, 30 min, P | [3H]-Spiperone,  0.2 nM (0.09 nM) | (+)Butaclamol, 1 µM |  |
| Dopamine-D3 | Human | CHO | F, pH 7.7, 0.25 mL,  37°C, 60 min, T | [125I]-Iodosulpride,  0.2 nM (0.53 nM) | Risperidone, 1 µM | Sokoloff *et al*. 19905 |
| Dopamine-D4 | Human | L929 | C, pH 7.7, 0.5 mL,  37°C, 30 min, P | [3H]-Spiperone,  0.5 nM (0.16nM) | Haloperidol, 1 µM |  |
| Histamine-H1 | Human | CHO | D, pH 7.5, 0.5 mL,  25°C, 30 min, P | [3H]-Pyrilamine,  1 nM (1 nM) | Astemizole, 1 µM | Chang et al. 19786  Laduron et al. 19827 |
| Cholinergic- muscarinic | Rat | Striatum, TP | D, pH 7.5, 0.5 mL,  37°C, 30 min, P | [3H]-Dexetimide,  2 nM (0.51 nM) | Dexetimide, 1 µM | Laduron et al. 19798 |
| Dopamine-transporter | Rat | Striatum, TP | K, pH 7.4, 0.5 mL,  0°C, 60 min, P | [3H]-WIN35428,  2 nM (35 nM) | Mazindol, 1 mM | Madras et al. 19899 |
| Noradrenaline- transporter | Rat | Cortex, TP | K, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-Nisoxetine,  2 nM (1.86 nM) | Mazindol, 1 µM | Tejani-Butt, 199110 |
| Serotonin- transporter | Human | Platelets | L, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-Paroxetine,  0.5 nM (0.15 nM) | Imipramine, 1 µM | Mellerup et al. 198311 |
| Glycine1-transporter | Human | HEK293 | R, pH 7.4, 0.1 mL,  RT, 60 min, C | [14C]-Glycine,  10 µM (43 µM) | Sarcosine, 1 mM |  |
| Glycine2-transporter | Human | HEK293 | S, pH 7.4, 0.1 mL,  RT, 60 min, C | [14C]-Glycine,  10 µM (26 µM) | Glycine, 10 mM |  |
| NMDA-  MK801-site | Rat | Forebrain, TP | M, pH 7.4, 0.5 mL,  37°C, 60 min, P | [3H]-MK801,  + glycine 1 µM  + glutamate 1 µM,  3 nM (12 nM) | Phencyclidine, 10 µM | Williams et al. 199212 |
| NMDA-glycine site | Rat | Forebrain, TP | M, pH 7.4, 0.5 mL, 0°C, 30 min, B | [3H]-Glycine,  + strychnine 100 µM,  20 nM (163 nM) | D-serine, 100 µM | Ogita et al. 198913 |
| AMPA-channel | Rat | Forebrain, TP | M, pH 7.4, 0.5 mL, 0°C, 60 min, B | [3H]-AMPA,  + KSCN 1 mM, 5 nM  (39 nM) | Glutamate, 1 mM | Honeré et al. 198214 |
| µ-Opiate | Human | CHO | A, pH 7.4, 0.5 mL, 25°C, 60 min, P | [3H]-DAMGO,  2 nM (0.64 nM) | Dextromoramide, 1 µM | Leysen et al. 198315 |
| δ-Opiate | Human | C6 glioma | E, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-DPDPE,  2 nM (2.0 nM) | Naltrindole, 1 µM | Gillan et al. 198016 |
| κ-Opiate | Guinea pig | Cerebellum, TP | A, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-U69593,  2 nM (1.15 nM) | Spiradoline, 1 µM | Lahti *et al*. 198517 |
| σ1 | Human | Sf9 | A, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-Haloperidol,  5 nM (6.3 nM) | DTG, 10 µM |  |
| CCK-A | Rat | Pancreas  TP | I, pH 7.4, 0.5 mL, 25°C, 30 min, P | [3H]-CCK8,  2 nM (3.15 nM) | CCK8, 1 µM | Chang and Lotti, 198618 |
| CCK-B | Human | C6 glioma | I, pH 7.4, 0.5 mL, 37°C, 30 min, P | [3H]-CCK8,  0.5 nM (0.23 nM) | L635260, 1 µM | Chang and Lotti, 198618 |
| Bradykinin-B2 | Human | CHO | T, pH 7.4, 0.5 mL,  25°C, 30 min, P | [3H]-Bradykinin,  0.5 nM (0.17 nM) | Bradykinin, 1 µM | Eggerickx *et al*. 199219 |
| NK1 | Human | CHO | E, pH 7.4, 0.5 mL,  25°C, 30 min, P | [3H]-Substance P,  0.5 nM (0.09 nM) | Substance P, 1 µM | Snider et al. 199120 |
| NK2 | Human | Sf9 | E, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-SR48968,  0.3 nM (0.34 nM) | SR48968, 1 µM | Emonds-Alt et al. 199321 |
| NK3 | Human | CHO | P, pH 7.4, 0.5 mL,  25°C, 60 min, P | [3H]-SR142801,  0.25 nM (0.26 nM) | Senktide, 1 µM |  |
| VIP | Human | CHO | Q, pH 7.4, 0.2 mL,  RT, 24 hours, S | [125I]-VIP,  0.05 nM (0.055 nM) | VIP, 1 µM |  |
| Neurotensin | Guinea pig | Forebrain | Y, pH 7.4, 1.1 mL,  25°C, 20 min, B | [3H]-Neurotensin,  1 nM (7.1 nM) | Neurotensin, 1 µM |  |
| Ca2+ channel | Rat | Cortex  M + L + P | A, pH 7.7, 0.5 mL,  37°C, 30 min, P | [3H]-Nitrendipine,  0.1 nM (0.23 nM) | Nifedipine, 1 µM | Murphy and Snyder, 198222 |
| Na+ channel | Rat | Cortex  M + L + P | G, pH 7.4, 0.5 mL, 37°C, 30 min, P | [3H]-Batrachotoxin B, + scorpion venom 3 µg/mL,  1 nM (500 nM) | Penfluridol, 1 µM | Pauwels et al. 198623 |
| Thromboxane-  A2 | Human | Platelets | V, pH 7.4, 0.25 mL,  37°C, 30 min, B | [3H]-SQ29548,  5 nM (7.8 nM) | SQ29548, 10 µM |  |
| Leukotriene D4 | Guinea pig | Lung  M + L + P | W, pH 7.4, 0.25 mL,  25°C, 30 min, B | [3H]-Leukotriene D4,  0.25 nM (0.28 nM) | ICI 198615  10 µM | Mong *et al*. 198524 |
| PAF | Rabbit | Platelets, TP | X, pH 7.4, 0.25 mL, 25°C, 30 min, B | [3H]-PAF,  0.5 nM (0.55 nM) | PAF, 1 µM | Hwang and Lam, 198625 |

aModifications to the assay conditions may have been made in comparison with those used in the original reference cited.

A: Tris-HCl 50 mM; B: Tris-HCl 50 mM, CaCl2 4 mM; C: Tris-HCl 50 mM, NaCl 120 mM, KCl 5 mM, MgCl2 1 mM, CaCl2 2 mM; D: Na-K phosphate 50 mM; E: Tris-HCl 50 mM, EGTA 1 mM, MgCl2 2 mM, BSA 0.1%; F: Tris-HCl 50 mM, NaCl 120 mM, KCl 5 mM, MgCl2 1 mM, CaCl2 2 mM, BSA 0.1%; G: HEPES-Tris 50 mM, choline chloride 130 mM, KCl 5.4 mM, MgSO4 0.8 mM, glucose 5.5 mM; H: Tris-HCl 20 mM, NaCl 154 mM; I: Tris-HCl 10 mM, NaCl 120 mM, MgCl2 10 mM, EGTA 1 mM, soybean trypsin inhibitor 50 µg/ml, bacitracin 0.2 mM, PMSF 10 µM, BSA 0.1%; J: glycylglycine-NaOH 25 mM; K: Tris-HCl 50 mM, NaCl 300 mM, KCl 5 mM; L: Tris-HCl 50 mM, NaCl 120 mM, KCl 5 mM; M: Tris-Acetate 50 mM; N: Tris-HCl 50 mM, MgCl2 10 mM, EGTA 1 mM, pargyline 10 µM; O: HEPES-NaOH 20 mM, NaCl 137 mM, KCl 2.7 mM, Na2HPO4 0.34 mM, KH2PO4 0.44 mM, NaHCO3 4.2 mM, PMSF 1 µM, BSA 0.1%; P: Tris-HCl 50 mM, MnCl2 3 mM, bacitracin 40 µg/ml, leupeptin 4 µg/ml, chymostatin 2 µg/ml, BSA 0.01%; Q: Tris-HCl 50 mM, MgCl2 10 mM, EGTA 1 mM, leupeptin 6 µg/ml, benzamidine 50 µM, pefabloc 0.4 mM, BSA 0.1%; R: HEPES 25 mM, K-gluconate 5.4 mM, Ca-gluconate 1.8 mM, MgSO4 0.8 mM, NaCl 140 mM, glucose 5 mM, L-alanine 5 mM; S: HEPES 25 mM, K-gluconate 5.4 mM, Ca-gluconate 1.8 mM, MgSO4 0.8 mM, NaCl 140 mM, glucose 5 mM, sarcosine 1 mM; T: Tris-HCl 50 mM, MgCl2 2 mM, DTT 1 mM, o-phenantroline 1 mM, bacitracin 0.1 mM, BSA 0.1%; U: Tris-HCl 50 mM, MgCl2 10 mM, EDTA 0.5 mM; V: Tris-HCl 50 mM, NaCl 120 mM, glucose 5 mM, indometacin 10 µM; W: Tris-HCl 10 mM, MgCl2 10 mM, CaCl2 10 mM, cysteine 5 mM, glycine 5 mM, BSA 0.15%; X: Tris-HCl 10 mM, MgCl2 10 mM, BSA 0.25%; Y: Tris-HCl 50 mM, o-phenanthroline 0.5 mM, EDTA 1 mM, BSA 0.1%.

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BSA, bovine serum albumin; CCK, cholecystokinin; CHO, Chinese hamster ovary cells; DAMGO, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin; DPDPE, [D- Pen2,D- Pen5] enkephalin; DTT, dithiothreitol; EDTA, ethylenediaminetetraacetic acid; EGTA, ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid; HEK, human embryonic kidney cells; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; KD, dissociation constant; KSCN, potassium thiocyanate; M+L+P, mitochondrial and microsomal fraction; NK, neurokinin; NMDA, N-methyl-D-aspartate; PAF, platelet-activating factor; PMSF, phenylmethylsulfonyl fluoride; Tris, trisaminomethane; TP, total particulate membrane function; VIP, vasoactive intestinal peptide.

**Table S2. Binding assay conditions used for 5-HT receptors.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Species/receptor** | **Cell line/tissue** | **Radioligand** | **Temperature (°C)/time (min)** | **Blank** | **Buffer** | **Referencesa** |
| h5-HT1A | L929 | [3H]8-OH-DPAT | 37/30 | Spiroxatrine | D |  |
| h5-HT1B | HEK293 | [3H]alniditan | 37/30 | Sumatriptan | E |  |
| h5-HT1D | C6glioma | [3H]alniditan | 37/30 | Sumatriptan | E | Waeber *et al*. 198826 |
| h5-HT1e | L929 | [3H]5-HT | 25/60 | 5-HT | A |  |
| h5-HT1f | HEK293 | [3H]5-HT | 25/60 | 5-HT | A |  |
| h5-HT2A | L929 | [125I]R093274 | 37/60 | BW501 | E | Mertens et al. 199427 |
| h5-HT2B | CHO | [3H]5-HT | 25/60 | Ritanserin | A |  |
| h5-HT2C | Sf9+Gαq+βy | [3H]mesulergine | 25/30 | Ritanserin | D | Pazos *et al*. 198428 |
| h5-HT3 | NxG 108CC15 | [3H]GR65630 | 37/60 | ICS 205–930 | F | Hoyer and Neijt, 198729 |
| h5-HT4(b)/(a) | HEK293 | [3H]prucalopride | 25/60 | 5-HT | A | Grossman et al. 199330 |
| h5-HT4(b)/(a) | HEK293 | [3H]5-HT | 25/60 | GR113808 | A |  |
| h5-HT5a | HEK293 | [3H]5-CT | 25/60 | Methiothepin | A |  |
| h5-HT6 | HEK293/CHO | [3H]5-HT | 25/60 | Methiothepin | B |  |
| 5-HT7 | CHO | [3H]5-HT | 25/60 | Risperidone | A |  |

aModifications to the assay conditions may have been made in comparison with those used in the original reference cited.

A: 50 mM Tris/HCl, pH 7.4, 1 mM EGTA, 10 mM MgCl2, 10 µM pargyline. B: 50 mM Tris/HCl, pH 7.4, 1 mM EGTA, 5 mM MgCl2, 10 µM pargyline. C: 50 mM HEPES/NaOH, pH 7.4. D: 50 mM Tris/HCl, pH 7.4, 4 mM CaCl2. E: 50 mM Tris/HCl, pH 7.4, 120 mM NaCl, 5 mM KCl, 1 mM MgCl2, 2 mM CaCl2. F: 20 mM Tris/HCl, pH 7.4, 154 mM NaCl.

5-CT, 5-carboxamidotryptamine; 5-HT, 5-hydroxytryptamine; CHO, Chinese hamster ovary cells; EGTA, ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid; HEK, human embryonic kidney cells; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; Tris, trisaminomethane.

**Table S3. List of behavioural and CNS-related assessments performed in each of the pharmacology, safety pharmacology and toxicology studies.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Year of study | Animal species | Sample size | Behavioural and CNS-related assessments |
| Interaction of prucalopride with pentylenetetrazol | | | | |
| R4437M-SPD555 | 1996 | Wistar rats (female) | Pre-treated with prucalopride, *n*=5; pre-treated with solvent, *n*=5 | Pentylenetetrazole-induced tremors, tonic and clonic convulsions and mortality were assessed. |
| Behavioural assessments performed during pharmacology studies in mice, rats and dogs | | | | |
| M4358M-SPD555 | 1996 | Swiss mice (male); Wistar rats (male and female); beagle dogs (male and female) | Mice, *n*=5 per dose; rats, *n*=3–5 per dose; dogs, *n*=5 per dose (solvent-treated control animals were also included) | In mice and rats, changes in the following behaviours and body functions were assessed: sniffing, licking, rearing, preening, chewing, excitation, tremors, convulsions, lacrimation, salivation, diarrhoea, piloerection, passivity, sedation, prostration, catalepsy, ataxia, hypnosis, pinna and cornea reflexes, muscle tone, dyspnoea, hot plate reaction time and acetic acid writhing.  In dogs, overt changes in the following behavioural phenomena were assessed: salivation, lacrimation, defecation, diarrhoea, vomiting, hyperventilation, ataxia, loss of righting, catalepsy, vocalization, excitation, aggressiveness, tremors and convulsions. |
| Behavioural assessments performed during cardiovascular safety pharmacology studies in dogs | | | | |
| D4434M-SPD555 | 1993 | Beagle dogs (male) | Prucalopride, *n*=7; solvent, *n*=7 | Changes in the following behaviours were assessed: wakefulness, abnormal posture, respiration, sedation, agitation, excitation, aggression, convulsions, relaxation of the lower eyelids, vomiting, urination and defecation. |
| D4435M-SPD555 | 1999 | Beagle dogs (male) | Prucalopride, *n*=9; solvent, *n*=9 |
| D4436M | 1993 | Beagle dogs (male) | Prucalopride, *n*=7; solvent, *n*=7 |
| Behavioural and CNS-related assessments performed during single-dose toxicity studies | | | | |
| M4476M-SPD555 | 1995 | Swiss mice (male and female) | Prucalopride, 5 males and  5 females per dose groupa/solvent | Clinical observations of lethality and gross behavioural effects included: ptosis, convulsions, tremors, salivation, sedation, ataxia and hypothermia. |
| R4479M-SPD555 | 1993 | Wistar rats (male and female) | Prucalopride, *n*=6; solvent, *n*=4 |
| R4480M-SPD555 | 1995 | Wistar rats (male and female) | Prucalopride, *n*=10; solvent, *n*=10 |
| Behavioural and CNS-related assessments performed during repeated-dose toxicity studies | | | | |
| M4889M-SPD555 | 2000 | Swiss mice (male and female) | Prucalopride, *n=*360; control, *n=*120 (n=60 per dose group) | Clinical observations for signs of waning health, abnormal behaviour or unusual appearance, occurrence of untoward clinical effects and manifestations of toxic and pharmacological responses, moribund state and mortality, included: ptosis, convulsions, tremors, salivation, sedation, ataxia and hypothermia. |
| R4491M-SPD5555 | 1997 | Wistar rats (male and female) | Prucalopride, *n*=80; control, *n*=20 (*n*=20 per dose group) |
| R4892M-SPD555 | 2000 | Wistar rats (male and female) | Prucalopride, *n=*360; control, *n=*120 (*n=*60 per dose group) |
| D4503M-SPD555  (One-month repeated dose oral toxicity study) | 1997 | Beagle dogs (male and female) | Prucalopride, *n*=16; control, *n*=4 (*n*=4 per dose group) | Clinical observations for signs of waning health, abnormal behaviour or unusual appearance, occurrence of untoward clinical effects and manifestations of toxic and pharmacological responses, moribund state and mortality, included: ptosis, photophobia, decubitus, pedalling movements, salivation, sedation and biting behaviour. |
| D4507M-SPD555  (12-month repeated dose oral toxicity study) | 1998 | Beagle dogs (male and female) | Prucalopride, *n=*24; control, *n=*8 (*n=*8 per dose group) |

CNS, central nervous system.

**Table S4. Mean concentrations of unchanged drug in various tissues of non-pregnant female rats after a single oral dose of prucalopride 5 mg base-equivalent/kg.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Concentration of unchanged drug (µg-equivalent/g)** | | | | | | | |  |
| **Tissue** | **20 min (*n=*3)** | **1 h (*n=*3)** | **3 h (*n=*3)** | **8 h (*n=*3)** | **24 h (*n=*3)** | **48 h (*n=*3)** | **AUC0–8 h (µg-equivalent\*h/g)** | **AUC0–8 h tissue:plasma ratio** | |
| Brain | 0.08 | 0.15 | 0.047 | 0.01 | <0.01 | <0.01 | 0.433 | 0.49 | |
| Heart | 0.97 | 1.31 | 0.34 | 0.05 | <0.02 | <0.02 | 3.54 | 4.00 | |
| Lung | 2.14 | 3.33 | 0.92 | 0.15 | <0.01 | <0.01 | 9.09 | 10.3 | |
| Liver | 6.86 | 3.65 | 1.10 | 0.25 | <0.01 | <0.01 | 12.8 | 14.4 | |
| Kidney | ND | 4.31 | 1.28 | 0.19 | <0.01 | <0.01 | 11.4 | 12.9 | |
| Adrenal gland | 3.6 | 4.26 | 1.06 | <0.20 | <0.20 | <0.20 | 8.53a | 13.5a | |
| Stomach tissue | 8.6 | 5.41 | 0.92 | 0.12 | <0.01 | <0.01 | 15.0 | 17.0 | |
| Small intestine | 10.1 | 6.32 | 2.60 | 0.48 | <0.01 | <0.01 | 23.8 | 26.9 | |
| Large intestine | 0.89 | 1.72 | 0.86 | 0.31 | <0.01 | <0.01 | 6.52 | 7.37 | |
| Muscle | 0.75 | 1.10 | 0.36 | 0.05 | <0.01 | <0.01 | 3.24 | 3.67 | |

aAUC0–3 h value or ratio.

One rat was inadvertently dosed twice; the 96-h group data are thus not reported.

AUC0–3 h, area under the concentration *versus* time curve from 0 to 3 hours; AUC0–8 h, area under the concentration *versus* time curve from 0 to 8 hours; ND, not determined.

**Table S5. ED50 of pentylenetetrazol in rats pretreated with prucalopride or solvent.**

|  |  |  |
| --- | --- | --- |
|  | **ED50 (95% CI) of intravenous pentylenetetrazol, mg/kg** | |
| **Effect** | **Solvent** | **Prucalopride 40 mg/kg** |
| Tremors  Score ≥1  Score ≥2  Score ≥3  Score = 4 | 11 (8.0–14)  11 (8.0–14)  16 (12–22)  16 (12–22) | 8.2 (6.0–11)  9.4 (6.9–13)  14 (12–17)  14 (12–17) |
| Clonic convulsions  Score ≥1  Score ≥2  Score ≥3  Score = 4 | 28 (21–38)  28 (21–38)  28 (21–38)  28 (21–38) | 21 (16–29)  21 (16–29)  28 (23–35)  28 (23–35) |
| Tonic convulsions: fore paws  Score ≥1  Score ≥2  Score ≥3  Score = 4 | 32 (24–44)  32 (24–44)  32 (24–44)  32 (24–44) | 37 (27–50)  37 (27–50)  37 (27–50)  43 (32–58) |
| Tonic convulsions: hind paws  Score ≥1  Score ≥2  Score ≥3  Score = 4 | 32 (24–44)  32 (24–44)  43 (26–69)  40 (30–80) | 37 (27–50)  37 (27–50)  43 (32–58)  43 (32–58) |
| Mortality | 43 (32–58) | 65 (48–88) |

Scores: 1, weak and delayed; 2, weak but immediate; 3, pronounced but delayed; 4, pronounced and immediate.

CI, confidence interval; ED50, 50% effective dose.

**Table S6. Patient demographics in clinical studies evaluating safety associated with prucalopride.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Demographic** | **Placebo**  **(*n*=1973)** | **Prucalopride 0.5 mg**  **(*n*=110)** | **Prucalopride 1 mg**  **(*n*=330)** | **Prucalopride 2 mg**  **(*n*=1516)** | **Prucalopride 4 mg**  **(*n*=1349)** | **Prucalopride total  (*N*=3305)** | **Overall total**  **(*N*=5728)** |
| Age, years, mean (SD) | 47.8 (15.97) | 50.2 (20.43) | 54.9 (20.81) | 48.6 (16.84) | 48.1 (15.52) | 49.1 (17.00) | 48.6 (16.63) |
| Sex, n (%) | | | | | | | |
| Female | 1569 (79.5) | 95 (86.4) | 279 (84.5) | 1180 (77.8) | 1175 (87.1) | 2729 (82.6) | 4298 (81.4) |
| Male | 404 (20.5) | 15 (13.6) | 51 (15.5) | 336 (22.2) | 174 (12.9) | 576 (17.4) | 980 (18.6) |
| Race, n (%) | | | | | | | |
| White | 1583 (80.2) | 105 (95.5) | 312 (94.5) | 1194 (78.8) | 1175 (87.1) | 2786 (84.3) | 4369 (82.8) |
| Non-white | 381 (19.3) | 5 (4.5) | 18 (5.5) | 313 (20.6) | 174 (12.9) | 510 (15.4) | 891 (16.9) |
| BMI, kg/m2, mean (SD)a | 25.0 (5.27) | 25.2 (5.27) | 24.0 (4.10) | 25.0 (4.74) | 25.6 (5.33) | 25.1 (4.97) | 25.1 (5.08) |

aPlacebo, *n*=1965; prucalopride 0.5 mg, *n*=110; prucalopride 1 mg, *n*=330; prucalopride 2 mg, *n*=1513; prucalopride 4 mg, *n*=1342; Prucalopride total, *N*=3295; Overall total, *N*=5260.

BMI, body mass index; SD, standard deviation.

**Supplementary methods for rat tissue distribution studies**

*High-performance liquid chromatography*

A high-performance liquid chromatography (HPLC) method was developed to determine the concentration of prucalopride-base in animal tissues. Alkalinized tissue samples were extracted with toluene and analysed using reverse-phase HPLC with fluorescence detection at excitation and emission wavelengths of 280 nm and 340 nm, respectively. The limit of quantification was 10 ng/g. Standard curves were linear in the concentration ranges evaluated (10–10,000 ng/g). The mean overall coefficient of variation between runs, as obtained from independently prepared quality control samples (16.6–864 ng/ml), ranged from 4.5% to 5.7%. No degradation of the compound occurred when stored for 12 months at −20°C, after three freeze–thaw cycles, or after 72 hours at room temperature.

**Supplementary methods for behavioural and CNS-related assessments**

*Hot plate tests in mice*

Mice or rats were dropped onto a hot plate (55.0±0.1°C) within a cylinder of 10 cm in diameter. The reaction time to the licking or jumping response of the animal was measured (in 0.1 seconds after the first contact with the hot plate) before and 15, 30, 45 and 60 minutes after administration of prucalopride. Inhibition of response was defined as a reaction time of more than 20 seconds (<1% false positives) and blockade of response was defined as a reaction time of more than 30 seconds (cut-off time, 0% false positives).

*Traction tests in mice*

The animal was placed on a grid and subjected to continuously increasing traction. The resistance to traction of the grasping mouse obtained in the second of two trials was read from a scale graduated in g of pulling force. The test was performed before and 15, 30, 45 and 60 minutes after administration of the test compound, and evaluation of the drug effect was based on a comparison with the reading before treatment. Drug-induced increases in muscle tone were defined as greater than 30 g for slight hypertonia (<2% false positives) and as greater than 40 g for pronounced hypertonia (0% false positives). Drug-induced decreases in muscle tone were defined as greater than 40 g for slight hypotonia (3.5% false positives) and as greater than 50 g for pronounced hypotonia (1.7% false positives).

*Anticonvulsant activity against maximal electroshock in mice*

Electroshock (corneal electrodes; pulse frequency, 300/second; pulse train duration, 200 msec; pulse width, 1 msec; output, 20 mA)-induced convulsions were evaluated 85 minutes after administration of test compound. The scoring system was: 0, no inhibition of tonic or clonic convulsions; 1, inhibition of tonic convulsions of the hind paws; 2, complete inhibition of tonic convulsions (fore and hind paws); and 3, absence of both tonic and clonic convulsions.

*Measurement of palpebral opening in rats*

Palpebral opening was assessed before and 1, 2 and 3 hours after administration of test compound. The scoring system for palpebral opening was: (6) marked exophthalmos; (5) exophthalmos; (4) wide open; (3) three-quarters open; (2) half open; (1) one-quarter open; and (0) closed. Two scores were recorded at each time point, one before and one after manipulation of the animal. A drug-induced increase in palpebral opening was defined in accordance with the following criteria: (A) before manipulation: a score of 3 for a slight increase (0.7% false positives) and a score greater than 3 for a marked increase (0% false positives); (B) after manipulation: a score of 6 (not observed in controls). A drug-induced decrease in palpebral opening was assessed after manipulation in accordance with the following criteria: a score of 3 for a decrease (0.13% in controls) and a score of less than 3 for a marked decrease (not observed in controls).

*Acetic acid-induced writhing in rats*

Prucalopride or solvent was administered orally or subcutaneously 15 minutes after injection of acetic acid (1%; 0.5 mL) to rats that displayed at least 10 writhes within the first 10 minutes of acetic acid injection. Writhes counted between 45 and 60 minutes after administration of prucalopride or solvent were evaluated. Inhibition was defined as fewer than 17 writhes and blockade was defined as the absence of writhes.

*Motor activity tests in rats*

Horizontal and vertical motor activity, the total number of movements and the total force were recorded over a period of 27 minutes, 1 hour after administration of test compound, using microprocessor-based activity monitors. Drug-induced depression was defined using the following criteria: fewer than 1300 counts for horizontal activity (1.5% false-positive controls), fewer than 80 counts for vertical activity (2.3% false positives), fewer than 2250 counts for total number of movements (1.3% false positives) and fewer than 1100 counts for total force (3.8% false positives). Drug-induced stimulation was defined using the following criteria: more than 3700 counts for horizontal activity (2.5% false-positive controls), more than 500 counts for vertical activity (3.2% false positives), more than 9500 counts for total number of movements (2.6% false positives) and more than 5300 counts for total force (3.4% false positives).

*Tail withdrawal test in rats*

Tail withdrawal reaction time (in seconds) after exposure of the tail to hot water (50±1°C) was measured 1 hour after administration of the test compound. Inhibition of the response was defined as a tail withdrawal time of longer than 5 seconds and blockade of the response was defined as a tail withdrawal time of longer than 10 seconds.

*Body temperature measurements in rats*

Body temperature was measured before and 1, 2 and 3 hours after the administration of prucalopride or solvent using an oesophageal probe and an Ellab Type TE3 electronic thermometer (Ellab, Hengelo, Netherlands). Drug-induced hypothermia and drug-induced marked hypothermia were defined as a decrease in body temperature of 2°C (0.1% false positives) and 3°C (0.03% false positives) compared with pretreatment body temperature, respectively. Drug-induced hyperthermia and drug-induced marked hyperthermia were defined as an increase in body temperature of 1°C (0.2% false positives) and 2°C (not observed in controls) compared with pretreatment body temperature, respectively.

*Measurement of pupil diameter in mice and rats*

The pupil diameter of one eye was measured in 1/25 mm units using a microscopic micrometre before and after administration of prucalopride. In mice, slight miosis and pronounced miosis were defined as a drug-induced decrease in pupil diameter of fewer than 7 units (<2% false positives) and fewer than 5 units (0% false positives), respectively. Slight mydriasis and pronounced mydriasis were defined as a drug-induced increase in pupil diameter of more than 20 units (2% false positives) and more than 30 units (0% false positives), respectively. In rats, slight miosis and pronounced miosis were defined as a drug-induced decrease in pupil diameter of 5 units (2.1% false positives) and fewer than 5 units (0.13% false positives), respectively. Mydriasis and marked mydriasis were defined as a drug-induced increase in pupil diameter of more than 20 units (not observed in controls) and more than 50 units, respectively.

*Instrumentation of dogs*

Dogs were surgically instrumented after sedation with Hypnorm (1 mL/kg subcutaneously; fluanisone 10 mg/mL and fentanyl citrate 0.315 mg/mL; Johnson & Johnson, Beerse, Belgium) and anaesthesia with sodium pentobarbital (10 mg/kg intravenously). Anaesthesia was maintained with a mixture of nitrous oxide and oxygen in a ratio of 72:25. A left thoracotomy was performed through the fifth intercostal space. In order to measure left ventricular pressure, a catheter-tip micromanometer (JSI-400, Johnson & Johnson Scientific Instruments Division, Beerse, Belgium) was positioned in the left ventricle through a stab wound in the apex and secured on the heart. An electromagnetic flow probe (JSI-0276, Johnson & Johnson Scientific Instruments Division, Beerse, Belgium) was mounted on the pulmonary artery for the measurement of cardiac output. The left circumflex coronary artery was dissected free from surrounding tissue, and an ultrasonic Doppler flow probe was placed around the vessel. A Tygon catheter was inserted into the descending aorta for recording aortic blood pressure. The leads of the implanted devices were exteriorized at the dorsal side of the neck.

The animals were allowed to recover from the surgical intervention and were trained to accept laboratory procedures before being enrolled in pharmacological experiments.

**Supplementary Information**

**Independent ethics committee / institutional review board information**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical trial ID (ClinicalTrials.gov identifier)** | **Name of ethics committee /review board** | **Location of review** | **Review date** |
| PRU-BEL-6 (NCT00576511) | Commission for Medical Ethics (Clinical Research) | Universital Hospital Gasthuisberg, Herestraat 49, 3000, Leuven, Belgium | 20 October 1994 |
| PRU-FRA-1 (Not registered) | Consultative Committee for the Protection of People Enrolled in Biomedical Research (CCPPRB) | Centre Hospitalier de Sain-Germain-en-Laye, 20 rue Armagis, 78105, Saint-Germain-en-Laye, France | 22 February 1996 |
| SPD555-302  (NCT01147926) | Central Ethics Committee Belgium | Commissie Medische Ethiek van Universitaire Ziekenhuizen K.U.Leuven Herestraat 49, 3000, Leuven, Belgium | NA |
| Ethics Committee for Multicentral Clinical Trials | 5 Sveta Nedelya Square, 1000, Sofia, Bulgaria |
| Etická komise (MEC / LEC for site 300011) | FN Hradec Králové LF UK a VLF JEP Sokolská 581, 500 05 H. Králové, Czech Republic |
| Etická komise (Site 300007) | Krajska Nemocnice T. Bati a.s. Havlickovo nabrezi 600 762 75 Zlin, Czech Republic |
| Etická komise (Site 300008) | MONSE, spol. s.r.o. Bělohorská 188/157 16900 Praha 6, Czech Republic |
| Etická komise (site 300009) | Usteckoorlicka nemocnice a.s. CS.armady 1076 562 18 Usti nad Orlici, Czech Republic |
| Etická komise (Site 300012) | Nemocnice Karlovy Vary a.s. Bezrucova 19 360 01 Karlovy Vary, Czech Republic |
| Etická komise FNKV (Site 300016) | FN Královské Vinohrady Šrobárova 50 100 34 Praha 10, Czech Republic |
| Etická komise (Site 30018 and Site 300019) | FN v Motole V Uvalu 84 150 06, Praha 5, Czech Republic |
| De Videnskabsetiske Komiteer Region Hovedstaden Regionsgården (The Committees on Biomedical Research Ethics for the Capital Region) | Kongens Vænge 2 3400 Hillerød, Denmark |
| Comitè de Protetion des Personnes -CCP SUD MEDITERRANEEV | C.H.U.-Hopital de Cimiez B.P. 1179 06003 Nice Cedex 1, France |
| Central Ethics Committee Ethik-Kommission der sächsischen Landesärztekammer | 150010Schützenhöhe 1601099 Dresden, Germany |
| Central Ethics Committee Netherlands Secretariaat medisch-ethische toetsingscommissie azM/UM | Oxfordlaan 10 Maastricht 6229 HX, the Netherlands |
| Komisja Bioetyczna Uniwersytetu Medycznego w Lublinie | Al. Racławickie 1 20-950 Lublin, Poland |
| Central Ethics Committee | Ministerul Sanatatii Comisia Nationala de Etica Pentru Studiul Clinic al Medicamentului Str Av. Sanatescu st48., sector 1 011478 Bucuresti, Romania |
| NRES Committee West Midlands – Edgbaston | The Old Chapel Royal Standard Place Nottingham, NG1 6FS, UK |
| SPD555-401  (NCT01424228)  SPD555-401  (NCT01424228)  (*continued*)  SPD555-401  (NCT01424228)  (*continued*) | Universitaire Ziekenhuizen Gasthuisberg, Commissie Medische Ethiek, | Herestraat 49, Campus Gasthuisberg E330, Leuven, 3000, Flemish Brabant, Belgium | NA |
| Commission d’Ethique Biomédicale | Hospitalo-Facultaire, Avenue Hippocrate 10, Woluwe, 1200, Brussels, Belgium |
| Comitè d’Ethique CHU Sart-Tilman Domaine | Universitaire du Sart-Tilman, 1 Avenue de I’Hôpital, Liège, 4000, Belgium |
| Etická komise Orlickoústecká nemocnice, Cs | Armády 1076, Ústí nd Orlicí, 562 18, Czech Republic |
| Eticka komise Nemocnice Tabor, a.s. | Kapitana Jarose 2000, Tabor, 390 02, Czech Republic |
| Eticka komise Oblastni nemocnice Kolin a.s | Zizkova 146, Kolin, 280 20, Czech Republic |
| Etická komise Krajská nemocnice Liberec | Liberec, Liberecký kraj, 460 63, Czech Republic |
| Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága | Arany János utca 6-8, Budapest, H-1051, Hungary |
| Comitato Etico dell’Università Campus Bio-Medico di Roma | Via A. Del Portillo, 21, Roma, 00128, Italy |
| Comitato di Bioetica Policlinico San Matteo | Viale Golgi n° 19, Pavia, 27100, Italy |
| Comitato Etico dell’Azienda Policlinico Umberto 1 di Roma | Viale del Policlinico, 155, Roma, 00161, Italy |
| Comitato Etico Dell’IRCCS Istituto Clinico Humanitas di Rozzano | Via Manzoni, 56, Rozzano, Milano, 20089, Italy |
| Comitato Etico Azienda Ospedaliera Universitaria San Martino Genova | Largo Rosanna Benzi 10, Genova, 16132, Italy |
| Comitato Etico per la Sperimentazione dell’Azienda Ospedaliera di Padova | Via Giustiniani 1, Padova, 35128, Italy |
| Komisja Bioetyczna przy Okregowej Izbie Lekarskie | ulica Krupnicza 11a, Kraków, Malopolskie, 31-123, Poland |
| Academia de Stiinte Medicale-Comisa Nationala de Etica Pentru Studiul Clinic al Medicamentului | Strada Aviator Sanatescu, Nr. 48, Sector 1, Bucuresti, 011478, Romania |
| Etická Komise Nitranského Samosprávného Kraja | Štefánikova 69, Nitra, 94901, Slovakia |
| Nezavisla eticka komisa Bratislavskeho samospravneho kraja | Sabinovska 16, Bratislava, 8 21 02, Slovakia |
| Úrad žilinského Samosprávneho Kraja, Etická Komisia | ulica Komenského 48, Žilina, 01109, Slovakia |
| Eticka komisia pri Diabetol s.r.o. | Hlavna 60, Presov, 080 01, Slovakia |
| Etická komisia, Úrad Košického samosprávneho kraja, | Námestie Maratónu Mieru 1, Košice, 042 66, Slovakia |
| Nezavisla eticka komisia Trnavskeho samospravneho kraja | Starohajska 10, Trnava, 917 01, Slovakia |
| Nezavisla eticka komisa Bratislavskeho samospravneho kraja | Sabinovska 16, Bratislava, 821 02, Slovakia |
| Comite Etico de Investigacion Clinica Complejo Hospitalario Nuestra Señora de Valme | Carretera Cadiz-Bellavista, km 548.9, Planta Baja, Secretaría Administrativa/Dirección Económico-Administrativa, Sevilla, 41041, Spain |
| Comité Autonómico de Ensayos Clínicos de Andalucía | Avenida de la Innovación, s/n, Edificio Arena 1, Sevilla, 41071, Spain |
| Comite Etico de Investigacion Clinica | Parc Taulí, s/n, Edificio Victoria Eugenia, Sabadell, Barcelona, 08208, Spain |
| Comite Etico de Investigacion Clinica del Hospital Clinico San Carlos | Calle Profesor Martín Lagos s/n, Madrid, 28040, Spain |
| Regionala Etikprövningsnämnden I Göteborg | Guldhedsgatan 5A, hus 2, plan 4, Göteborg, 413 20, Sweden |
| PRU-GBR-4  (NCT00575614) | Harrow Ethics Research Committee | Physiology Unit St Mark’s Hospital, North wick Park, Watford Road, Harrow, Middlesex, HAI3UJ, UK | 21 April 1997 |
| PRU-INT-1  (NCT00617513) | Ethikkommission der Medizinischen Fakultät Graz | Landeskrankenanstalt Graz  II. Medizinische Abteilung Auenbruggerplatz I A-8036 Graz, Austria | NA |
| Ethikkommission des Krankenhauses der Stadt Wien-Lainz | Krankenhaus der Stadt Wien-Lainz, I. Medizinische Abteilung Wolkersbergenstrasse I A-1130 Wien, Austria |
| Ethikkommission der Krankenanstalt der Stadt Wien – Rudolfstiftung | Krankenanstalt der Stadt Wien Rudolfstiftung 4. Mcdizinische Abteilung Juchgasse 25 A-1030 Wien, Austria |
| Ethikkommission des Krankenhauses der barmherzigen Schwestern vom heiligen Kreuz | Krankenhaus der barmherzigen  Schwestern vom heiligen Kreuz I. Interne Abteilung Grieskirchner Strasse 42 A-4600 Wels, Austria |
| Ethikkommission der Medizinischen Fakultät Graz | Ordination ftir Innere Medizin St. Veiter Strasse 2 A-9020 Klagenfurt, Austria |
| Ethikkommission der Medizinischen Fakultät Graz | A.ö. Landeskrankenhaus  Deutschlandsberg Medizinische Abteilung  Radlpass-Strasse 29  A-8530 Deutschlandberg, Austria |
| Ethikkommission der Medizinischen  Fakultät der Universität Wien | Universitaetsklinik für Innere Medizin IV  Klinische Abteilung für Gastroenterologie und Hepatologic  Währinger Gürter 18–20  A-1090 Wien, Austria |
| Ethikkommission der Medizinischen Fakultät Graz | A.ö. Krankenhaus der Stadt Bludenz  Chirurgische Abteilung  Spitalgasse 13  A-6700 Bludenz, Austria |
| PRU-INT-12  (NCT00487422) | Ethikkommision der Österreischischen Arbeitsgemeinschaft für klinische Pharmakologie und Therapie und der privaten Krankenanstalt Institut für Hypertoniker  *Change of ethic committee:*  Ethikkommission für klinische Prüfungen außerhalb von Krankenanstalten für das Bundesland Wien | Geriatrierentrum am Wienerwald 4. Medizinische Abteilung mit geriatrischer Rehabilitation Jagdschlossgasse 59 A-1130, Wien, Austria | 19 February 1999 |
| Amt der Niederösterreichischen Landesregierung NÖ Ethikkommission | Ordination: Arzt für Allgemeinmedizin Kindlergasse 4  A-2700 Wr. Neustadt, Austria | 23 March 1999 |
| PRU-INT-2  (NCT00631813)  PRU-INT-2  (NCT00631813)  (*continued*)  PRU-INT-2  (NCT00631813)  (*continued*) | Ethikkommission der Medizinischen Fakultät Graz | Landeskrankenstalt Graz  II. Medizinische Abteilung  Auenbruggerplatz 1  A-8036 Graz, Austria | NA |
| Österreichische Arbeitsgemeinschaft für klinische Pharmakologie, Ethikkommission | A.ö. Landeskrankenhaus  Deutschlandsberg Medizinische Abteilung Radlpass-Strasse 29 A-8530 Deutschlandsberg, Austria |
| Ethikkommission im Hanusch Krankenhaus, Wiener Gebietskrankenkasse | Hanusch·Krankenhaus I. Medizinische Abteilung Heinrich-Collin-Strasse 30 A-1140 Wien, Austria |
| E.C. Onze-Lieve-Vrouwe Hospitaal | Site #1 Private Practice Maandagweg 29 8500 Kortrijk, Belgium  Sit#2 Private Practice Gretrystraat 33  2018 Antwerpen, Belgium |
| Medisch Ethische Commissie | Academisch Medisch Centrum  Meibergdreef 9  1105 AZ Amsterdam, the Netherlands |
| Toetsingscommissie Klinisch Geneesmiddelenonderzoek | Sint Jans Gasthuis  Vogelsbleek 5  6001 BE Weert, the Netherlands |
| Medisch Ethische Toetsingscommissie | Rode Kruis Ziekenhuis  Vondellan 13  1942 LE Beverwijk, the Netherlands |
| Subcommissie medische experimenten met mensen | Bosch Medicentrum  Niuewstraat 34  5211 NL DEN BOSCH, the Netherlands |
| Commissie Toetsing Wetenschappelijk | Algemeen Christelijk Ziekenhuis Eemland  Utrechtseweg 160  3818 EW AMERSFOORT, the Netherlands |
| Toetsingscommissie | Ikazia Ziekenhuis  Montessoriweg 1  3083 AN ROTTERDAM, the Netherlands |
| Medisch ethische commissie | St. Ziekenhuis Bronovo-Nebo  Bronovolaan 5  2597 AX DEN HAAG, the Netherlands |
| Toetsingscommissie Onderzoek | Stichting Ziekenhuiscentrum Apeldoorn  Albert Schweitzerlaan 31  7334 DZ APELDOORN, the Netherlands |
| Regional komité for medisinsk forskningsetikk  Universitetet i Bergen | Medisinsk A vdeling  Diakonissehjemmet  Diakonissehjemmets sykehus  Haraldsplass  BERGEN, 5009, Norway |
| Same as above | Medisinsk avdeling  Regionsykehuset i Trondheim  7006 Trondheim, Norway |
| Same as above | Medisinsk avdeling  Kongsvinger sykeh  Kongsvinger sykehus  2200 Kongsvinger, Norway |
| Same as above | Medisinsk avdeling  Haukeland sykehus  5021 Bergen, Norway |
| Clindepharm Ethical Committee | Kingsbury Hospital  Wilderness Road  Clarement  7700, South Africa |
| Same as above | Milpark Hospital  Suite 202-2nd floor  Guild Road  Parktown  2193, South Africa |
| Same as above | Milpark Hospital  Suite E  Guild Road  Parktown  2193, South Africa |
| Same as above | Parklands Hospital  Medical Mews 4  Hopelands Road  Durban  4001, South Africa |
| Same as above | Nedpark Medical Center 401  Trevanna Street  Sunnyside  0132, South Africa |
| Same as above | Suite E  Rochester Place  173 Rivonia Road  Morningside  2146, South Africa |
| The University of the Orange Free State  Faculty of Medicine | Universitas Hospital  Department of Internal Medicine  Bloemfontein  9300, South Africa |
| Research Protocol and Ethics Committee  The University of Pretoria  Faculty of Medicine | Gastrointestinal Clinic  H F Verwoerd Hospital  Dr savage Road  Pretoria  0001, South Africa |
| Uppsala universitet Medicinska fakultetens forskningsetikkommitte Inst for obstretik och gynekologi  Akadmiska sjukhuset | Dept. of Surgery  Akademiska sjukhuset  751 85 UPPSALA, Sweden  Dept. of Medicine  Universitetssjukhuset  221 85 LUND, Sweden  Dept. of Surgery  Danderyds sjukhus  182 88 DANDERYD, Sweden  Dept. of Medicine  Reionsjukhuset  701 85 ÖREBRO, Sweden  Dept. of Surgery  SU/Östra sjukhuset  416 85 GÖTEBORG, Sweden  Mage-tarm klin  Universitetssjukhuset  581 85 LINKÖPING, Sweden  Gastroenheten  Huddinge sjukhus  141 86 HUDDINGE, Sweden |
| PRU-INT-6  (NCT00488137)  PRU-INT-6  (NCT00488137)  (*continued*)  PRU-INT-6  (NCT00488137)  (*continued*)  PRU-INT-6  (NCT00488137)  (*continued*)  PRU-INT-6  (NCT00488137)  (*continued*) | The Northern Sydney Area  Health Service  Royal North Shore Hospital  Campus  Human Research Ethics  Committee | Dept of Medicine  Level 3, Wallace Freeborn Building  Royal North Shore Hospital  Pacific Highway  ST LEONARDS NSW 2065, Australia | 20 July 1998 |
| Hunter Area Research Ethics Committee | John Hunter Hospital  NEW LAMBTON HEIGHTS  NSW 305, Australia | 29 April 1998 |
| The South Eastern Sydney Area  Health Service- Southern  Section  St. George Hospital Campus  Ethics Committee | Dept of Gastroenterology  St George Hospital  Gray Street  KOGARAH NSW 2217, Australia | 28 April 1998 |
| The Alfred Health Care Group Ethics Committee | Dept of Gastroenterology  The Alfred  Commercial Road  PRAHRAN VIC 3181, Australia | 23 April 1998 |
| Sir Charles Gairdner Hospital Institutional Ethics Committee | Dept. of Gastroenterology  Sir Charles Gairdner Hospital  Verdun Street, Nedlands,  WA 6009, Australia | 9 January 1998 |
| Clinical Research and Ethics Committee | Dept Medicine  Western Hospital  Footscray  Vic 3011, Australia | 22 April 1998 |
| Mater Hospital Research Ethics Committee | University Department of Medicine Administration Centre, 1st Floor  Mater Adult Hospital  Raymond Terrace  SOUTH BRISBANE QLD 4101, Australia | 11 August 1998 |
| Commissie voor Medische Ethiek | Private Practice  Coupure Rechts 316  900 Gent, Belgium | NA |
| Ethisch Comité O-L-Vrouwziekenhuis | O-L-Vrouwziekenhuis  Moorselbaan 164  9300 Aalst, Belgium | 5 November 1998 |
| Commissie voor Medische Ethiek OCMW Antwerpen | Grétrystraat 33  2018 Antwerpen, Belgium | 11 February 1998 |
| Commissie voor Medische ethiek O-L-Vrouwhospitaal | Private Practice  O-L-Vrouwhospitaal  Maandagweg 29  8500 Kortrijk, Belgium | 10 February 1999 |
| Unite de recherche clinique  Campus Saint-Luc- CHUM | Campus Saint-Luc- CHUM  Pavilion Edouard-Asselin  Unite de recherche clinique  05 264, Rene Levesque est - Bureau 105 G  Montreal, Quebec  H2X 1P1, Canada | 11 March 1998 |
| Comité de déontologie  Health Sciences Review Board Centre Universitaire de Santé | Centre de Recherche  Centre Universitaire de Sante  L'Estrie Fleurimont  3001- 12e ave. N.  Sherbrooke, QC JIH 5N4, Canada | 1 June 1998 |
| Queen's University Health  Sciences Review Board | Hotel Dieu Hospital  166 Brock Street  Kingston, ON K7L 5G2, Canada | 7 April 1998 |
| Research Ethics Committee | QEII- Health Sciences Centre  Room 9-018 Victoria Building  Victoria General Hospital  1278 Tower Road  Halifax. NS B3H 2Y9, Canada | 26 February 1998 |
| University of Western Ontario  Review Board for Health Sciences Research Involving Human Subjects | St. Joseph's Health Centre  268 Grosvenor St.  London, ON N6A 4V2, Canada | 31 March 1998 |
| Comite d'Ethique de la recherche | Centre Hospitalier  Universitaire de Quebec  II, cote du Palais  Quebec,QC  GIR 2J6, Canada | 24 March 1998 |
| Committee on Scientific Dev.  McMaster University | McMaster University  4W8- 1200 Main Street W.  Hamilton, ON L8S 4J9, Canada | 25 February 1998 |
| Research Ethics Board | Hy’s Medical Centre  Walter McKenzie Centre  University of Alberta  Suite 310- 11010 101st St. N.W.  Edmonton, AB TSH 4B9, Canada | 27 February 1998  4 March 1999 |
| Research Ethics Board | Robert Newton Research Building  Walter McKenzie Centre  University of Alberta  519- 63 University Campus NW  Edmonton, AB T6G 2S2, Canada | NA |
| Faculty Committee on the Use of Human Subjects in Research | University of Manitoba  Health Sciences Centre  GB 443–820 Sherbrook ST.  Winnipeg, MB, R3A 1R9, Canada | 23 February 1998 |
| Chesapeake Research Review, Ind. | Group North Windsor  200–2462 Howard Avenue  Windsor, ON N8X 3V6, Canada | 25 June 1998 |
| Toetsingscommissie Klinisch Geneesmiddelenonderzoek | Sint Jans Gasthuis  Vogelsbleek 5  6001 BE WEERT, the Netherlands | 18 February 1998 |
| Medische Ethische Commissie | Stichting Ziekenhuis Amstelveen  Laan van de Helende Meesters 88  1186 AM AMSTELVEEN, the Netherlands | NA |
| Medische Ethische Commissie – Subcommissie Mengsebonden Onderzoek | Stichting Christelijk Ziekenhuis Refaja  Boerhaavestraat 1  9501 HE STADSKANAAL, the Netherlands | 30 March 1998 |
| Commissie Toetsing Wetenschappelijk Onderzoek | Algcmeen Christelijk Ziekenhuis Eemland  Utrechtseweg 160  3818 ES AMERSFOORT, the Netherlands | NA |
| Medisch Ethische Commissie | Academisch Medisch Centrum  Meibergdreef 9  1105 AZ Amsterdam, the Netherlands | NA |
| Subcommissie voor de ethiek van het mensgebonden onderzoek | Academisch Ziekenhuis Vrije Universiteit De Boelelaan 1117  1081 HV AMSTERDAM, the Netherlands | 9 March 1998 |
| Medisch Ethische Commissie | Martini Ziekenhuis, lokatie Van Swieten  Posthus 30033  9700 RM GRONINGEN, the Netherlands | 19 February 1998 |
| Toetsingscommissie Medisch Wetenschappelijk Onderzoek | Reinier de Graaf Gashuis/SSDZ  Reinier de Graafweg 3–11  2625 AD DELFT, the Netherlands | 17 March 1998 |
| Medisch Ethisce Commissie | Atrium Ziekenhuis, lokatie Gregorius  Koehstraat 2  6442 BE BRUNSSUM, the Netherlands | 22 June 1998 |
| Medisch Ethische Commissie | Stichting Streekziekenhuis Midden-Twente  Geerdinksweg 141  7555 DL HENGELO, the Netherlands | 16 June 1998 |
| Commissie Wetenschappelijk Onderzoek bij Mensen | Academisch Ziekenhuis Utrecht  Heidelberglaan 100  3584 CX UTRECHT, the Netherlands | 1 July 1998 |
| Regional komité for medisinsk forkskningsetikk | Medisinsk avdeling  Gastroenterologisk seksjon  Haukelnd sykehus  5021 BERGEN, Norway | 16 April 1998 |
| Same as above | Medisinsk avdeling  Gastroenterologisk seksjon  Regionsykehuset i Trondheim  7005 TRONDHEIM, Norway | 16 April 1998 |
| Same as above | Medisinsk avdeling  Diakonhjemmets sykehus  PB 23 Vindem  0319 OSLO, Norway | 16 April 1998 |
| Same as above | Gastromedisinsk avdeling  Ullevål sykehus  0407 OSLO, Norway | 16 April 1998 |
| Pharma-Ethics | Kingsbury Hospital  Fairfield Medical Suites  Wilderness Road  Claremont  Cape Town, South Africa | 17 February 1998 |
| Same as above | Milpark Hospital  Suite 202 2nd floor  Parktown 2006, South Africa | 17 February 1998 |
| Same as above | Milpark Hospital  Medical Suite E  Parktown 2006, South Africa | 17 February 1998 |
| Same as above | Parklands Hospital  Medical Mews 4  Hopelands Road  Durban 4001, South Africa | 17 February 1998 |
| Same as above | 401 Nedpark Medical Centre  Trevanna Street  Sunnyside 0132, South Africa | 17 February 1998 |
| University of the Orange Free State Ethics Committee | Universitas Hospital  Department of Internal Medicine  Bloemfontein 9300, South Africa | 24 March 1998 |
| University of Cape Town Ethics | Groote Schuur Hospital  Department of Gastroenterology  Cape Town, South Africa | 31 March 1998 |
| University of Stellenbosch Ethics | Tygerberg Hospital  Department of Gastroenterology  Bellville  Cape Town, South Africa | 13 March 1998 |
| Forskningsetikkommittén Inst för kvinnors och barns hålsa  Obstetrik & gynekologi  Akademisk sjukhuset | Kirugiska klinien  Akademiska sjukhuset  721 85 UPPSALA, Sweden | 27 January 1998 |
| Same as above | Mag-tarm mottagningen  Regionsjukhuset  701 85 ÖREBRO, Sweden | 9 January 1998 |
| Same as above | Kirurgkliniken  Centralsjukhuset  651 85 KARLSTAD, Sweden | 26 February 1998 |
| Same as above | Kirurgkliniken  Södersjukhuset  118 83 STOCKHOLM, Sweden | 26 February 1998 |
| Same as above | Kirurgkliniken  Kärnsjukhuset  541 85 SKÖVDE, Sweden | 23 March 1998 |
| Same as above | Gastroenheten  Medicinkliniken  Mälarsjukhuset  631 88 ESKILSTUNA, Sweden | 26 February 1998 |
| Same as above | Kirurglkliniken  Centrallasaretter  351 85 VÄXJÖ, Sweden | 26 February 1998 |
| Same as above | Kirurgkliniken  Länssjukhuset ryhov  551 85 JÖNKÖPING  Sweden | 26 February 1998 |
| The Ethics committee  Stepping Hill Hospital | Stepping Hill Hospital  Poplar Grove  STOCKPORT  Cheshire SK2 7JE, UK | 2 March 1998 |
| Merton, Sutton & Wandsworth Local  Research Ethics Committee | St Helier Hospital  WrytheLane  CARSHALTON  Surrey SM5 1AA, UK | 18 March 1998 |
| Research Ethics Committee City Hospital NHS trust | Birmingham City Hospital  Dudley Road  BIRMINGHAM  Bl8 7QH, UK | 18 September 1998 |
| Hull & East Riding LREC | University of Hull  Castle Hill Hospital  Castle Hill  COTTINGHAM  N Humberside HU16 SJQ, UK | 20 July 1998 |
| LREC  Royal Free Hospital & Medical School | Royal Free Hospital  Pond Street  LONDON  NW3 2QG, UK | 16 December 1998 |
| Research Ethics Committee  Leeds Health Authority/United Leeds Teaching Hospital | Leeds General Infirmary  Great George Street  LEEDS  LS1 3EX, UK | 9 October 1998 |
| Ethics (Medical) Research Committee  Professional Unit | Beaumont Hospital  Beaumont Road  DUBLIN 9, IRELAND | 17 April 1998 |
| Tayside Committee on Medical Research Ethics | Ninewells Hospital & Medical School  DUNDEE  DD1 9SY, UK | 25 September 1998 |
| Southampton & SW Hants Joint LREC | Southampton General Hospital  Tremona Road  SOUTHAMPTON  SO16 4XY, UK | 27 April 1998 |
| Ethics Committee | University of Nottingham  Queens Medical Centre  NOTTINGHAM  NG7 2UH, UK | 2 March 1998 |
| South Manchester LREC  Manchester Health Authority | Withington Hospital  Nell Lane  WEST DIDSBURY  MANCHESTER  M20 7LR, UK | 25 August 1998 |
| PRU-CRC-3001  (NCT01116206)  PRU-CRC-3001  (NCT01116206)  (*continued*)  PRU-CRC-3001  (NCT01116206)  (*continued*) | Human Research Ethics Committee | John Hunter Hospital  Level 2, Department of  Gastroenterology, Lookout Road, New Lambton, NSW, 2305, Australia | NA |
| Melbourne Health Human Research Ethics Committee | The Alfred Hospital  Department of Gastroenterology,  Ward 4B, Level 4, Main Block, Commercial Road, Melbourne, VIC, 3004, Australia |
| Institutional Review Board, Taipei Veterans General Hospital | Taipei Veterans General Hospital, No.201, Sec.2, Shih-Pai Road, Taipei, 11217, Taiwan |
| The 1st Affiliated Hospital Sun YAT University Ethics Committee | 1st The Affiliated Hospital Sun YAT University, No. 58, Zhongshan Er Road,  Guangzhou, Guangdong Province, 510080, China |
| Severance Hospital, Yonsei University College of Medicine | Severance Hospital  Yonsei University Health System, 250 Seongsanno, Seodaemun-gu, Seoul, 120-752, Korea |
| The Catholic University of Korea Seoul St.Mary's Hospital | Seoul St. Mary's Hospital  505 Banpo-dong, Seocho-gu, Seoul, 137-701, Korea |
| Wonkwang University Hospital | Won Kwang University Hospital  344-2, ShinYong-Dong,  Ik-San, Chon Buk, 570-711, Korea |
| Human Research Ethics Committee | St George Hospital  Department of Gastroenterology,  St George Hospital, 1 South St Kogarah, NSW, 2217, Australia |
| Sir Run Run Shaw Hospital, Affiliated with School of Medicine, Zhejiang University Ethics  Committee | Sir Run Run Shaw Hospital, Affiliated with School of Medicine, Zhejiang University, No.3 Qingchun East Road,  Hangzhou, Zhejiang Province, 310016, China |
| The 2nd Affiliated Hospital Ethics Committee to Xian Jiaotong University | The 2nd Affiliated Hospital to Xian Jiaotong University, No 157 Xiwu Road, Xian, Shanxi Province, 710004, China |
| Xi Nan Hospital Ethics Committee | Xi Nan Hospital, No. 35, Gaotanyanzheng Street, Shapingba District, Chongqing, 400038, China |
| 1st The Affiliated Hospital, College of Medicine, Zhejiang University Ethics  Committee | 1st The Affiliated Hospital, College of Medicine, Zhejiang University  No. 261, Qing Chun Street  Hangzhou, Zhejiang, 310003, China |
| The Institutional Review Board, Faculty of Medicine, Chulalongkorn University | Chulalongkorn Hospital  Division of Gastroenterology,  Department of Internal Medicine, Chulalongkorn University 1873, Rama 4 Road, Patumwan,  Bangkok, 10330, Thailand |
| Beijing Chaoyang Hospital Ethics Committee | Beijing Chaoyang Hospital  No.8, Baijiazhuang, Chaoyang District, Beijing, 100020, China |
| Melbourne Health Human Research Ethics Committee | Royal Melbourne Hospital  Department of Gastroenterology, 3 Centre, Level 3, Main Block, Grattan Street  Parkville, VIC, 3052, Australia |
| Research Ethics Committee, Royal Adelaide Hospital | Royal Adelaide Hospital  Department of Gastroenterology and  Hepatology, Q7, North Wing, North Terrace  Adelaide, SA, 5000, Australia |
| Tongji medical College, Huazhong Science Technology University Ethics Committee | Union Hospital, Tongji Medical College, Huazhong Science, Technology University, No. 1277 Jiefang Avenue, Wuhan, Hubei Province, 430022, China |
| Institutional Review Board, Royal Thai Army Medical Department | Pramongkutklao Hospital  General Clinical Research Center of Phramongkutklao Hospital and College of Medicine, 315 Ratchawithi Road, Phayathai Rachadevee, Bangkok, 10400, Thailand |
| Kyungpook National University Hospital | KyungPook University Hospital, KyungPook Univ, Hospital 200, Dongduk-Ro, Jung-Gu, DaeGu, 700-721, Korea |
| Chungnam National University Hospital | Chungnam University Hospital, 640 Daesadong Jung-gu, Daejeon, 301-721,  Korea |
| Asan Medical Center | Asan Medical Center  86 Asanbyeongwon-gil,  Songpa-gu, Seoul, 138-736, Korea |
| Ewha Woman’s University Mokdong Hospital | Ewha Womans University,  MokDong Hospital, 911-1 Mokdong Yangcheon-Gu,  Seoul, 158-710, Korea |
| Human Research Ethics Committee | Nepean Hospital  Nepean GI group, Suite 107, 64-68 Derby Street  Kingswood, NSW, 2747, Australia |
| Peking Union Medical College Hospital IEC | Peking Union Medical College Hospital,  No. 1 Shuaifuyuan, Wangfujing, Dongdan,  Beijing, 100070, China |
| Human Research Ethics Committee Sydney West Area Health Service  Nepean Hospital | Royal North Shore Hospital  Department of Gastroenterology,  Level 11E, Main Block, Royal, North Shore Hospital, Pacific Highway,  St. Leonards, NSW, 2065, Australia |
| KyungHee University Hospital | Kyung Hee University Medical Center 1 Hoegi-dong, Dongdaemun-gu,  Seoul, 130-702, Korea |
| Seoul National University Hospital | Seoul National University Hospital, Department of Internal Medicine, 28  Yongon-Dong, Chongno-Gu, Seoul, 110-744, Korea |
| Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects Faculty of  Medicine, Ramathibodi Hospital, Mahidol University | Ramathibodi Hospital  Division of Gastroenterology,  Department of Medicine, Faculty of Medicine, Ramathibodi Hospital,  RamaVI Road, Payathai,  Bangkok, 10400, Thailand |
| Siriraj Institutional Review Board (SiRB) | Siriraj Hospital  Division of Gatroenterology,  Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand |
| Qilu Hospital, Shandong University Ethics Committee | Qilu Hospital, Shandong University, No. 107, Wenhua West Road, Jinan, Shandong Province, 250012, China |
| 1st JiangSu Province Hospital, the Affiliates Hospital with Nanjing Medical University Ethics Committee | 1st JiangSu Province Hospital, the Affiliates Hospital with Nanjing  Medical University, No. 300, Guangzhou Road,  Nanjing, Jiangsu province, 21002,9 China |
| Melbourne Health Human Research Ethics Committee | Box Hill Hospital  Level 2, 5 Arnold Street  Box Hill, VIC, 3128, Australia |
| Chonnam National University Hospital | Chon-Nam National University Hospital,  8 Hak-dong, Dong-gu,  Gwangju, 501-757, Korea |
| Samsung Medical Center | Samsung Medical Center  Department of Internal Medicine, 50. Ilwon dong, Kangnam-ku, Seoul, 135-710, Korea |
| Pusan National University Hospital | Pusan National University Hospital 3 FL., B Building, 305 Gudeok-Ro, Seo-Gu (1 Ga,Ami-dong) Busan, 602-739, Korea |
| Peking University 1st Hospital National Clinical Trial Ethics Committee | Peking University 1st Hospital, No. 8 Xishiku Street, Beijing, 100034, China |
| Ethic Committee of Zhong Shan Hospital | Zhongshan Hospital, Fudan University, No. 180 Fenglin Road, Shanghai, 200032, China |
| Mackay Memorial Hospital  Institutional Review Board | Mackay Memorial Hospital Tamsui Branch, No. 45, Minsheng Rd., Tamsui Town, Taipei, 21560, Taiwan |
| First Affiliated Hospital of Fourth Military Medical University Ethics Committee | Xijing Hospital,the Fourth Military Medical University  No. 169 Changle West Road, Xian, Shanxi province, 710032, China |
| National Taiwan University Hospital Research Ethics Committee | National Taiwan University  Hospital, No.7, Chung Shan South Road, Department of Internal Medicine, Taipei, 100, Taiwan |
| Beijing Friendship Hospital attached to the CAPITA Ethics Committee | Beijing Friendship Hospital attached to the CAPITA  No 95, Yong'an Street, Xuanwu District, Beijing, 100100, China |
| The 1st Affiliated Hospital of Anhui Medical University Ethics Committee | The 1st Affiliated Hospital of Anhui Medical University  No218 Ji-Xi Roda, Hefei, Anhui Province, 230022, China |
| Chinese PLA general Hospital Medical Ethics Committee | Chinese PLA general Hospital, #28 Fuxing Road,  Beijing, 100853, China |
| Ruijin Hospital Ethics Committee | Ruijin Hospital, No 197 Ruijin Er Road, Shanghai, 200025, China |
| Shanghai Changhai Hospital Ethics Committee | Shanghai Changhai Hospital No.168 Changhai Road, Shanghai, 200433, China |
| Peking University 3rd Hospital Clinical Trial Ethics Committee | Peking University 3rd Hospital, No 49 Huayuan Bei Road, Haidian  District, Beijing,100071, China |
| PRU-USA-11  (NCT00483886)  PRU-USA-11  (NCT00483886)  (*continued*)  PRU-USA-11  (NCT00483886)  (*continued*) | University of Michigan Medical  School Institutional Review Board | The University of Michigan Medical School, 2432 Medical Science Building-1  Ann Arbor, Michigan 48109-0605, USA | NA |
| Mayo Clinic Institutional Review Board | Mayo Clinic  200 First St. S.W.  Rochester MN 55905, USA | 4 August 1998 |
| Western Institutional Review Board | Medical Arts Building, Suite 202 24 - Second Avenue, W.E., Hickory NC 28601, USA | NA |
| Human Subjects Committee  University of Arizona | University of Arizona  Health Science Center  Dept of Internal Medicine  Section of Gastroenterology,  Tucson, Arizona 85724-5137, USA | NA |
| Western Institutional Review Board | Wilson Digestive Diseases Center, P.A.  Wilson, NC 27893, USA | 26 March 1998  19 March 1998 |
| Western Institutional Review Board | Piedmond Medical Research Assocs.  1901 S. Hawthrone Rd., Ste. 306, Winston-Salem, NC 27103, USA | 23 February 1998 |
| Porter Adventist Hospital Littleton  Adventist Hospital Join Institutional Review Board | 2535 S. Downing St. Suite 360, Denver, CO 80210-5850, USA | NA |
| Western Institutional Review Board | New Hanover Medical Research Associates  4302 Holly Tree Road,  Wilmington, NC 28412, USA | 27 March 1998  17 February 1998 |
| Springfield Committee for Research Involving Human Subjects | Southern Illinois University School of Medicine, Memorial Medical Centre  St John’s Hospital, Dept. of Internal, USA  Medicine/Gastroenterology, Springfield, Illinois 62794-1215, USA | 30 March 1998 |
| Western Institutional Review Board | Wichita Clinic, 3311 E. Murdock, Wichita, KS 67208, USA | 5 March 1998 |
| Western Institutional Review Board | Family Medicine East,  7602 East Harry Street,  Wichita, KS 67207, USA | 23 June 1998  17 February 1998 |
| Western Institutional Review Board | The Center for GI Research, 9707 Medical Center Dr., Suite 310, Rockville, MD 20850, USA | 19 March 1999 |
| Western Institutional Review Board | West Hill Gastroenterology Assoc., PC 9155 S.W. Barnes Road, Suite 636, Portland, OR 97225, USA | 12 March 1998 |
| Western Institutional Review Board | Gastroenterology group of the Palm Beaches P.A., 2015 N. Flagler Drive, West Palm Beach, FL 33407, USA | 19 March 1999 |
| Western Institutional Review Board | Raleigh Community Hospital, 3400 Wake Forest Road,  Raleigh, NC 27609, USA | 14 December 1998  20 March 1998  12 February 1998 |
| Western Institutional Review Board | 2097 Henry Tecklenburg Drive, Suite 311,  Charleston, SC 29414-5733, USA | 19 March 1998 |
| Western Institutional Review Board | Center for Gastrointestinal Disorders, 1150 N 35th Ave., Suite 445, Hollywood, FL 33021-5430, USA | 16 March 1998 |
| The Cleveland Clinic Foundation  Institutional Review Board | The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA | 7 April 1998 |
| Committee on Clinical Investigations | Beth Israel Deaconess Medical Center, East Campus, 330 Brookline Avenue, Boston, MA 02215, USA | 1 February 1998 |
| Western Institutional Review Board | Center for Clinical Research-Austin  12221 MoPac Expressway, North Austin, TX 78758, USA | 17 August 1998  11 March 1998  26 February 1998  12 February 1998 |
| Women's Hospital Institutional Review Board | The Woman’s Hospital of Texas, 7580 Fannin, Suite 305, Houston, Texas 77054, USA | 17 February 1998 |
| Western Institutional Review Board | University of California, Irvine Medical Center  101 the City Drive  Diagnostic Center  Orange, CA 92868, USA | 16 March 1998 |
| Western Institutional Review Board | Oklahoma Foundation for Digestive Res.  711 Stanton L. Young Blvd., Ste. 619,  Oklahamoa City, OK 73104, USA | 16 March 1998 |
| Schulman Associates Institutional | TriCities Medical Research Associates  321 Midway Medical Park, Suites 3 & 5  Bristol, TN 37620  Bristol Regional Medical Center  1 Medical Park Blvd.  Bristol, TN 37620  Bristol Medical Associates  Suite 200E 1 Medical Park Blvd.  Bristol, TN 37620, USA | 18 May 1998  13 May 1998  1 April 1998  5 April 1998 |
| Schulman Associates Institutional | Wisconsin Center for Advanced Research  1000 E Layton Avenue, Suite 200, Milwaukee WI S3207, USA  Gastroenterology Consultants Ltd, 2901, West Kinnickinnie River Parkway, Suite 570, Milwaukee, WI 53215, USA  Center for Digestive Health  2901 W. Kinnickinnie River Parkway, Suite S60, Milkwaukee, WI 53215, USA | 18 February 1998 |
| Hanover General Hospital | Hanover Hospital  195 Stock St., Suite 203  Hanover, PA 17731, USA | 19 March 1998 |
| Committee on Human Studies | West Los Angeles VA Medical Center  11301 Wilshire Blvd  Los Angeles, CA 90073, USA | 24 June 1998  13 April 1998 |
| Monroe Clinic Institutional Review Board | Monroe Clinic  411-22nd Ave. Monroe, WI 53566, USA | 20 March 1998 |
| UC Davis Human Subjects Review Committee | UC Davis General Medicine Research Group  2000 Stockton Blvd  Sacramento, CA 95817, USA  UCD Primary Care Network  2825 J. Street, Suite 300, Sacramento, CA 95815, USA  UCD Medical Center  Dept. Radiology, 2515 Stockton Blvd, Sacramento, CA 95817, USA | 18 February 1998 |
| Human Subjects Committee | Scripps Clinic/The Scripss Research Institute, Dept. of Gastroenterology  1066 North Torrey Pines Road  La Jolla, California 92037, USA | 9 July 1998 |
| Committee for the Protection of Human subjects | Dept. of Medicine  Trustees of Dartmouth College  Dartmouth-Hitchcock Medical Center  11 Rope Ferry Road  Hanover, NH 03755-1404, USA | NA |
| Biomedical Research Institute | Miami Research Associates Inc.  7500 S, W Ave.  Suite 200 & 202 Miami, FI 33173-5426, USA | 3 August 1998  17 February 1998 |
| Western Institutional Review Board | Physicians Research Center  601 Route 37 W., Ste. 104  Toms River, NJ 08755, USA | 19 March 1999  23 February 1998 |
| Virginia Physicians Inc. Institutional Review Board | McGuire Medical group  7702 Parham Road  Richmond Virginia 23294, USA | 3 March 1998 |
| Western Institutional Review Board | Clinical Studies, Providence  52 Amaral Street  East Providence RI 02915–2205, USA | 25 March 1999  19 March 1999  10 April 1998  17 February 1998 |
| Northwestern University Medical School Institutional Review Board | Northwestern Medical Faculty Foundation  Suite #822, 680 N. Lakeshore Drive  Chicago, lL 60611, USA | 20 March 1998 |
| University of Pittsburgh Institutional Review Board | University of Pittsburgh Medical Center  200 Lothrop Street, Mezzanine Level, e Wing, Pittsburgh, PA 15213, USA | 30 April 1998 |
| Committee on the Conduct of Human Research | Virginia Commonwealth University  Dept. of Gastroenterology  PO Box 980711  Richmond, Virginia, USA | NA |
| PRU-USA-13  (NCT00485940)  PRU-USA-13  (NCT00485940)  (*continued*)  PRU-USA-13  (NCT00485940)  (*continued*)  PRU-USA-13  (NCT00485940)  (*continued*) | The University of Tennessee, Memphis  Institutional Review Board | The University of Tennessee,  Memphis  Division of Gastroenterology  951 Court Avenue  Memphis, TN 38163, USA | NA |
| Western Institutional Review Board | 919 Westfall Road Suite B240  Rochester, New York 14618, USA | 17 February 1998 |
| University of Utah Health Sciences Center School of Medicine | Veterans Administration Hospital  500 Foothill Boulevard  GI Lab, Building 1, Salt Lake City, Utah 84148, USA | 16 March 1998 |
| Nalle Clinic Institutional Review Board | Nalle Clinic  1918 Randolph Road  Charlotte, NC 28207, USA | 13 February 1998 |
| Bio Medical Ethics Committee Institutional Review Board | Valley Presbyterian Hospital, 15107 Vanowen St. Van Nuys, CA 91405, USA | NA |
| Western Institutional Review Board | 8527 Village Drive. Suite 207, San Antonio, Texas 782 17–12501 Judson.  Suite 202, San Antonio, Texas 78233, USA | 17 September 1998 |
| The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals | Baylor College of Medicine  Department of Medicine – GI, 6550 Fannin, SM1122  Houston, Texas 77030, USA  The Methodist Hospital  6550 Fannin, SM849  Houston, Texas 77030, USA | 24 February 1998 |
| Institutional Review Board | Barnes-Jewish Hospital of St Louis, 216S Kingshighway, St. Louis, Missouri 63110, USA  Washington University School of Medicine  660 S. Euclid, St. Louis,  Missouri 63110, USA | 16 June 1998 |
| University Human Studies Committee | Department of Surgery  University of Louisville  550 South Jackson Street  Louisville, Kentucky 40202, USA  University Surgical Associates  601 S. Floyd, Suite 700, Louisville, Kentucky 40202,USA  Jewish Hospital  217E Chestnut Street  Louisville, Kentucky 40202, USA  Norton Hospital  200E Chestnut Street  Louisville, Kentucky 40202, USA | NA |
| Legacy Institutional Review Board | Legacy Portland Hospitals  Good Samaritan Hospital  1015 NW 22nd Portland, OR 97210, USA  Legacy Portland Hospitals  Emanuel Hospital  2801 N Gantenbein Ave.  Portland, OR 97227, USA | 14 August 1998  23 April 1998 |
| Western Institutional Review Board | Heart of America Research Institute, 5799 Broadmoor, Ste. 138, Mission, KS 66202, USA  Sunflower Medical Group  5555 West 58th Street, 930  Carondel Mission, KS 66202 K.C. 641, USA | NA |
| Western Institutional Review Board | Rockford Gastroenterology Associates  401 Roxbury Road, Rockford, Illinois 61107, USA | 10 June 1998 |
| Institutional Review Board Health Sciences Section | University of Missouri  Clinical Research Unit  N425 Health Sciences Center,  1 Hospital Drive, Colombia,  MO 65212, USA  University of Missouri  Endoscopy Center  NW401 Health Sciences Center, 1 Hospital Drive, Colombia, MO 65212, USA | 25 February 1998 |
| St. Jospeh’s Institutional Review Board | 4762 N. Habana Ave  Tampa, Fl 33614, USA  St. Joseph’s Comprehensive research  4200 N. Arnmenia Ave. Suite 3, Tampa, Fl 33607, USA | 26 February 1998 |
| Human Subject Protection Office | Gastroenterology and Hepatology Division  Hershey Medical Center  500 University Park Blvd.  Hershey, PA 17033–0850, USA | NA |
| Committee on Human Rights Research | New York Presbyterian Hospital – New York Weill  Cornell Center, 950 Park Avenue, New York, NY 10028, USA | 20 April 1998 |
| Western Institutional Review Board | Houston Institute for Clinical Research  7777 Southwest Freeway,  Suite 720, Houston, TX 77074, USA | 25 February 1998 |
| Western Institutional Review Board | 1492 East Broad Street  Suite 1404  Columbus, Ohio 43205, USA | 29 June 1998 |
| Western Institutional Review Board | Boulder Medical Centerr  2750 Broadway, Boulder, CO 80304, USA | 4 March 1999  11 February 1998 |
| Schulman Associates Institutional Review Board, Inc. | Mississippi Center for Clinical Research LLC  3000 Old Canton Road Suits 111, Jackson, MS 39216, USA  Gastrointestinal associates, PA  1421 North State Street, Suite 203, Jackson, MS 39202, USA  Mississippi Surgery Center  1421 North State Street, Jackson, MS 39202, USA | 23 September 1998 |
| Western Institutional Review Board | Doctor’s Clinic  2300 5th Avenue  Vero Beach, Fl 32960, USA  Doctor’s Clinic Sebastian  13840 US Hwy 1  Sebastian Fl 32958. USA  Doctor’s Clinic West  3850 20th Street  Vero Beach, Fl 32960, USA | NA |
| Abbot Northwestern Hospital IRB | Abbot Northwestern Hospital, 800 E 28th Street, Mpls, MN 55407, USA | NA |
| Human Research Review Committee | VA Medical Center  2100 Ridgecrest Drive SE  Albuquerque, New Mexico 87108, USA | NA |
| Human Subjects Committee | University of Kansas Medical Center  3901 Rainbow Boulevard  Kansas City, KS 66160, USA | 24 March 1998 |
| Western Institutional Review Board | R/D Clinical Research Inc.  135 Oyster Creek Drive, Suite W, Lake Jackson,  TX 77566, USA  Brazosport Memorial Hospital, 100 Medical Drive, Lake Jackson, TX 77566, USA | 23 February 1998 |
| Human Research Review Committee A. | Temple University  3401 N Broad Street,  Philadelphia, PA 19140, USA | 3 March 1998  2 March 1998 |
| Virginia Mason Research Center IRB | Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101, USA | 29 December 1998  5 August 1998  24 April 1998  3 May 1998 |
| Western Institutional Review Board | Nashville Medical Research Institute, LLC.  4320 Harding Road, Suite 309W, Nashville, TN 37205, USA  Nashville Medical Research Institute, LLC.  2010 Church Street, Suite 420, Nashville, TN 32705, USA  Nashville Medical Research Institute, LLC.  397 Wallace Road, Building C, Suite 407, Nashville, TN 32705, USA | NA |
| IRE | University of Nebraska Medical Center  600 So 42nd Street, Omaha, Nebraska 68198, USA | 19 February 1999 |
| Western Institutional Review Board | 555 Resevoir Drive, Suite 2020, San Diego, CA 92120, USA  Damluji Research Center  591 Camino de la Reina, Suite 410, San Diego, CA 92108, USA  5565 Grossmont Center Drive, Suite 227, La Mesa, CA 91942, USA  Alvarado Hospital Medical Center  6655 Alvarado Road, San Diego, CA 92120, USA | 10 April 1998  12 February 1998 |
| Western Institutional Review Board | Lynn Health Science Institute  5300 N. Independence, Suite 130, Oklahoma City, OK 73112, USA  608 NW 9th, Suite 6110, Oklahoma City, OK 73101, USA | 20 February 1998 |
| Institutional Review Board for Human Subject Protection | Baylor University Medical Center  3500 Gaston Avenue  Dallas, TX 75246, USA | 15 April 1998 |
| The Johns Hopkins Bayview Institutional Review Board for Human Research | Johns Hopkins Bayview Medical Center  4940 Eastern Avenue, Baltimore, MD 21224, USA | 15 June 1998 |
| Human Research Review Committee | Medical College of Wisconsin at Froedtert Memorial Lutheran Hospital  9200 W, Wisconsin Ave, Milwaukee, WI 53226, USA | NA |
| Western Institutional Review Board | 13303 Tesson Ferry Road,  Suite 35, St. Louis, Missouri 63011, USA | 4 March 1999  11 February 1999 |
| Western Institutional Review Board | Drug Research Services, Inc.  4720 South I-10 Service Road, Suite 501, Metairie, LA 70001, USA  Lakeside Hospital  400 South I-10 Service Road, Metairie, LA 70001, USA | 20 February 1998 |
| The Institutional Review Board of the Cleveland Clinic Foundation | The Cleveland Clinic Foundation  9500 Euclid Ave, Desk 540, Cleveland, OH 44195, USA | NA |
| Institutional Review Board | The University of Texas Medical Branch at Galveston  301 University Boulevard, Galveston, TX 77555–0674, USA | 5 October 1998 |
| Methodist Hospital IRB | Colon and Rectal Surgery Inc.  8712 W. Dodge Road, Suite 240, Omaha, NE 68114, USA | NA |
| Clinical Investigations Committee | Ochsner Clinic  1514 Jefferson Highway, New Orleans, LA 70121, USA | NA |
| Schulman Associates Institutional Review Board, Inc. | Keystone Digestive Disorders Consultants, PC, 4815 Liberty Avenue Suite M58, Pittsburgh, PA 15224, USA  The Western Pennsylvania Hospital, 4800 Friendship Avenue, Pittsburgh, PA 15224, USA | 23 September 1998 |
| PRU-USA-26  (NCT00627692)  PRU-USA-26  (NCT00627692)  (*continued*)  PRU-USA-26  (NCT00627692)  (*continued*) | Duke University Medical Center Institutional Review Board | Methodist Retirement Community, 2616 Erwin Road, Durham, NC 27705, USA | NA |
| Schulman Associates Institutional Review Board | Hewitt Memorial Hospital, 45, Maltbh Street, Shelton, CT 06484, USA  Gardner Heights, Inc., 172 Rocky Rest Road, Shelton, CT 06484, USA  Shelton Lakes Healthcare Center, 5 Lake Road, Shelton, CT 06484, USA  Mediplex of Milford, 245 Orange Avenue, Milfornd, CT 06460, USA | 24 February 2000  16 November 1999  27 October 1999  16 June 1999  3 February 1999 |
| Schulman Associates Institutional Review Board | East Mountain Manor, 101 East Mountain Boulevard, Wilkes-Barre, PA 18702, USA | 24 February 2000  27 October 1999  16 June 1999  27 January 1999 |
| Human Review Board | Dwight D. Eisenhower VA Medical Center, 4101 South 4th Street Trafficway, Leavenworth, KS 66048, USA | NA |
| Schulman Associates Institutional Review Board | Saint Ann’s Home, 9400 St. Ann’s Drive, Oklahoma City, OK 73161, USA  Mariner Health of Bethany, 6900 NW 39 Expressway, Bethany, OK 73008, USA  South Park Health Care, 5725 S. Ross Center, Oklahoma City, OK 73119, USA  Sweet Briar Nursing Center, 1400 Buena Vista, Midwest City, OK 73110, USA | 24 February 2000  27 October 1999  16 June 1999  22 January 1999 |
| Schulman Associates Institutional Review Board | Claiborne County Nursing Home, 1850 Old Knoxville Road, Tazewell, TN 37839, USA  Laurel Manor Health Care Facility, 902 Buchanan Road, New Tazewell, TN 37825, USA | 24 February 2000  27 October 1999  16 June 1999  22 January 1999 |
| Western Institutional Review Board | The Fredericksburg Nursing and Rehabilitation Center, 7602 Louis Pasteur Dr, San Antiono, Texas 78229, USA | 23 March 2000  16 March 2000  28 February 2000 |
| Schulman Associates Institutional Review Board | Parkside Rehabilitation and Care Center, 1230 Monitor, Wenatchee, WA 98801, USA  Colonial Vista Village Care and Rehabilitation Center, 625 Okanogan, Wenatchee, WA 98801, USA  Wenatchee Valley Clinic, Clinical Research Department, 820 North Chelan, Wenatchee, WA 98801, USA | 24 February 2000  27 October 1999  16 June 1999  28 April 1999 |
| Community Institutional Review Board | OSF Center for Senior Health, 200 East Pennsylvania Avenue, #L-01, Peoria, IL 61603-3089, USA  OSF St. Clare Home, 5533 North Galena Road, Peoria, IL 61614, USA  Lutheran Home, 7019 North Galena, Peoria, IL 61614, USA  Peoria Apostolic Home, 7023 North Galena Road, Peoria, IL 61614, USA | 4 August 1999 |
| Riverside Regional Convalescent Center | Riverside Regional Convalescent Center, 1000 Old Denbigh Blvd, Newport News, VA 23602, USA | NA |
| Schulman Associates Institutional Review Board | Fern crest Manor Nursing Facility, 14005 Haynes Boulevard, New Orleans, LA 70128, USA | 27 October 1999  16 June 1999  16 December 1999 |
| Schulman Associates Institutional Review Board | Regency Manor, 2000 Regency Manor Circle, Columbus, OH 43207, USA | NA |
| Schulman Associates Institutional Review Board | Howell/IHS Greenery, 3003 West Grand River Avenue, Howell, 1-11 48843, USA  Lahsor Hills Care Centre, 25300 Lahser Road, Southfield, MI 48034, USA | NA |
| Saint Joseph Health Center Institutional Review Board | Villa Saint Joseph of Garondelet Health, 11901 Rosewood, Overland Park, KS 66209, USA  Carondelet Manor of Carondelet Health, 621 Cardondelet Drive, KansasCity, MO 64114, USA | NA |
| Schulman Associates Institutional Review Board | Oakwood Terrace, 18905 Northeast 25th Avenue, North Miami Beach, FL 33180, USA  Palm Garden, 21251 East Dixie Highway, North Miami Beach, FL 33180, USA | NA |
| Western Institutional Review Board | University Park Manor, 4511 Coronado, Wichita Falls, TX 76310, USA  Horizon Manor, East Highway 82, Nocona, TX 76255, USA  Nocana Nursing Home, 306 Carolyn Road Nocona, TX 76255, USA  Olney Healthcare Center, 1002 West Payne Street, Olney, TX 76374, USA  Integrated Health Care Services of Wichita Falls, 601 Midwestern Parkway, Wichita Falls, TX 76302-2499, USA | 19 April 2000  28 February 2000  14 January 2000  9 December 1999  24 November 1999  22 October 1999  14 October 1999  15 July 1999  6 May 1999  15 March 1999  8 January 1999 |
| Schulman Associates Institutional Review Board | Bortz Health Care of Warren, 11700 East Ten Mile Road, Warren, MI 48089, USA | 27 October 1999  16 June 1999  24 February 2000  10 February 1999 |
| Schulman Associates Institutional Review Board | Springfield Residential Care Center, 2401 W. Grand Avenue, Springfield, MO 65802, USA  Christian Health Care of Nixa, 1104 N. Main, Nixa, MO 65714, USA  Bio-lEST Clinic, 2228 West College, Springfield, MO 65820 USA  Managed Health Care, 1947 West Sunset, Springfield, MO 65807, USA | 24 February 2000  27 October 1999  16 December 1998 |
| PRU-USA-3  (NCT00596596)  PRU-USA-3  (NCT00596596)  (*continued*) | The University of Tennessee/IRB | Gastroenterology Department, University of  Tennessee Medical  Center, 951 Court Avenue, Room 555 D, Memphis, TN 38163, USA | NA |
| University of Michigan Institution Board | The University of Michigan Medical Center, Department of Internal Medicine, Division of Gastroenterology, 1500 East Medical Campus Drive, 3912 Taubman Center, Ann Arbor, MI 48109, USA |
| Mayo Institutional Review Board | Mayo Clinic, Rochester, MN 55905, USA |
| Monroe Clinic IRB | The Monroe Medical Foundation for Research and Education, 515 22nd Avenue, Monroe, WI 53566, USA |
| Baylor College of Medicine  Affiliates Review Board for Human  Subject Research | Baylor College of Medicine, Smith Tower, Suite 1122, 6550 Fannin, Houston, TX 77030, USA |
| Western Institutional Review Board | Wilson Memorial Hospital, Inc., 1705 South Tarboro Street, Wilson, NC 27893, USA |
| All Saints Healthcare System Inc. Institutional Review Board | GI Consultants, 2901 West K.K. River Parkway, Suite 570, Milwaukee, WI 53215, USA |
| Dixie Medical Center Medical Review Board | Dixie Regional Medical Center, 544 South 400  East, St George, UT 84770, USA |
| Springfield Committee for Research Involving human Subjects | Memorial Medical Center, SIU School of Medicine, 800 North  Rutledge, Room Dl23, Springfield, IL 62781, USA |
| Western Institutional Review Board | Diabetes and Glandular Disease Clinic P.A.,  8042 Wurzbach, Suite 420, San Antonio, TX 78229, USA |
| Western Institutional Review Board | The Center for G I Research, 9707 Medical Center Drive,  Suite 310, Rockville, MD 20850, USA |
| Western Institutional Review Board | 1150 North 35th Avenue, Suite 445, Hollywood, FL 33021, USA |
| Western Institutional Review Board | 12221 North Mopac Expressway, 3rd Floor  Research, Austin,  TX 78758, USA |
| Committee on Human Studies | UCLA Neuroenteric Disease Sec., CURE Building 115,  Room213, WLA VAMC, 11301 Wilshire Blvd., Los Angeles, CA 90073, USA |
| Columbia Woman’s Hospital | Gastrointestinal Consultants of Houston, 7580  Fannin, Suite 305,  Houston, TX 77054, USA |
| Human Subjects Research  Committee | University of California Irvine Medical Center, 101 The City Drive, Orange, CA 92868, USA |
| Western Institutional Review Board | Oklahoma Foundation for Digestive Research, Suite 501, 711 Stanton L. Young Blvd., Oklahoma City, OK 73104, USA |
| Western Institutional Review Board | North Carolina Clinical Research, 4301 Lake Boone Trail, Suite 309A, Raleigh, NC 27607, USA |
| Hanover Hospital IRB | 195 Stock Street, Suite 203, Hanover, PA 17331, USA |
| Clayton Heydorn Institutional Review Board | Westchester County Medical Center, Valhalla, NY 10595, USA |
| Forsyth Memorial Hospital IRB | Piedmont Research Associates, 1901 South  Hawthorne Road, Suite 306, Winston-Salem, NC 27103, USA |
| The Johns Hopkins Bayview IRB for Human Research | The Johns Hopkins Bayview Medical Center, GI Department, 4940 Eastern Avenue, Baltimore, MD 21224, USA |
| Western Institutional Review Board | Drug Research Services, 4720 South I-10 Service Rd., Suite 501, Metaire, LA 70001, USA |
| Biomedical IRB | Presbyterian University Hospital, O'Hara at  DeSoto Streets, Pittsburgh, PA 15213, USA |
| Western Institutional Review Board | Associated Gastro Medical Group, West 1211 LaPalma, Suites 306 and 602, Anaheim, CA 92801, USA |
| Western Institutional Review Board | Long Beach Gastroenterology Association, 2650 Elm Avenue, Suite 201 and Annex, Long Beach, CA 90806, USA |
| PRU-USA-25a  (NCT00577018) | Western Institutional Review Board | Innovative Medical Research  1001 Cromwell Bridge Road, Suite 300, Towson, Maryland 21286, USA  4 West Rolfing Crossroads, Suite 1, Catonsville, Maryland 21228, USA | 18 June 1998 |
| Western Institutional Review Board | Innovative Medical Research  1950 Century Boulevard, Ste. 23, Atlanta, GA 30345, USA | 24 June 1998 |
| Western Institutional Review Board | Innovative Medical Research  2137 Welsh Road, #3C  Philadelphia, PA 19115, USA  Philadelphia Gastroenterology Consultants, Ltd.  700 Cottman Avenue, Suite 201, Philadelphia, PA 19111, USA  Northeast Imaging  8001 Roosevelt Blvd.  Smylie Times Bldg., Suite 104, Philadelphia, PA 19152, USA | 12 April 1999  23 September 1998  27 August 1998  2 July 1998 |
| PRU-USA-28  (NCT00598338)  PRU-USA-28  (NCT00598338)  (*continued*)  PRU-USA-28  (NCT00598338)  (*continued*)  PRU-USA-28  (NCT00598338)  (*continued*) | Western Institutional Review Board | Unifour Medical Research Associates  52 12th Avenue Place NE, Hickory, NC 28601, USA  Unifour Medical Research Associates  24 2nd Avenue NE, Suite 202, Hickory, NC 28601, USA  Catawba Radiological Associates, Inc.  Unifour Medical Commons, 18 13th Avenue NE, Hickory, NC 28601, USA | 5 October 1999 |
| Western Institutional Review Board | Doctor’s Clinic  2300 5th Avenue, Vero Beach, FL 32960, USA  Doctor’s Clinic Sebastian  13840 US Highway 1, Sebastian, FL 32958, USA  Doctor’s Clinic West  3850 20th Street, Vero Beach, FL 32960, USA | 28 April 1999 |
| The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals | Baylor College of Medicine  Department of Medicine – GI, 6550 Fannin, SM1122, Houston, TX 77030, USA  The Methodist Hospital  6550 Fannin, SM849, Houston, TX 77030, USA | 20 April 1999 |
| Research Review Committee A | Temple University Hospital  3401 North Broad Street, Philadelphia, Pennsylvania 19140, USA | 27 April 1999 |
| Quorum Review IRB | Piedmont Medical Research Associates  1901 S. Hawthorne Rd., Suite 306, Winston-Salem, NC 27103, USA  Forsyth Medical Specialists  PA 1901 S. Hawthorne Rd., Suite 310, Winston-Salem, NC 27103, USA | 8 October 1999  9 July 1999  7 April 1999 |
| Institutional Review Board | Barnes-Jewish Hospital of St. Louis  216S Kingshighway, St. Louis, Missouri 63110, USA  Washington University School of Medicine  660 S Euclid, St. Louis, Missouri 63110, USA | 12 May 1999 |
| University Human Studies Committee | Department of Surgery  University of Louisville, 550 South Jackson Street, Louisville, Kentucky 40202, USA  University Surgical Associates  601 S. Floyd, Suite 700, Louisville, Kentucky 40202, USA  Jewish Hospital  217E Chestnut Street, Louisville, Kentucky 40202, USA  Norton Hospital  200E Chestnut Street, Louisville, Kentucky 40202, USA | NA |
| Porter and Littleton Adventist Hospitals Joint Institutional Review Board | Centura Portercare Adventist Hospital  2535 S. Downing, Denver, CO 80210, USA  Araphoe Gastroenterology PC  2535 S. Downing, Suite 360, Denver, CO 80210, USA  Centura Littleton Adventist Hospital  7720 S. Broadway, Littleton, CO 80122, USA  Araphoe Gastroenterology PC  7720 S. Broadway, Suite 360, Littleton, CO 80122, USA | NA |
| Western Institutional Review Board | New Hanover Medical Research Associates  4302 Holly Tree Road, Wilmington, NC 28412, USA  New Hanover Medical Group PA  1960 South 16th Street, Wilmington, NC 28401, USA  Dr. Robert Hutchins Office  1915 S. 16th Street, Wilmington, NC 28401, USA | 4 October 1999  4 May 1999  5 April 1999 |
| Western Institutional Review Board | Rockford Gastroenterology Associates  401 Roxbury Road, Rockford, Illinois 61107, USA | 13 October 1999  20 April 1999 |
| Western Institutional Review Board | Keystone Digestive Disorder Consultants, PC  4815 Liberty Ave., Suite M58, Pittsburg, PA 15224, USA  The Western Pennsylvania Hospital  4800 Friendship Ave., Pittsburg, PA 15224, USA | 13 October 1999  18 May 1999  12 April 1999 |
| Institutional Review Board | University of Missouri Clinical Research Unit  N425 Health Sciences Center 1 Hospital Drive, Colombia, MO 65212, USA  University of Missouri Endoscopy Center  NW401 Health Sciences Center, 1 Hospital Drive, Colombia, MO 65212, USA | 28 April 1999  5 May 1999 |
| Western Institutional Review Board | West Hills Gastroenterology Associates PC  9155 SW Barnes Road, Suite 636, Portland, OR 97225, USA  West Hills Gastroenterology Associates PC  19250 SW 65th Street, Suite 355, Portland, OR 97062, USA | 5 October 1999  20 April 1999 |
| Western Institutional Review Board | Gastroenterology Group of the Palm Beaches PA  Waterside Clinical Research Services, Inc.  2015 North Flagler Drive, West Palm Beach, FL 33407, USA | 8 June 1999  4 May 1999  5 April 1999 |
| Western Institutional Review Board | Complete Colon Care  2097 Henry Tecklenburg Dr., Suite 311, Charleston, SC 29414, USA  Bon Secours St. Francis Hospital  2095 Henry Tecklenburg Dr., Suite 311, Charleston, SC 29414, USA | 3 May 1999 |
| Committee on Human Rights Research | New York Presbyterian Hospital – New York Weill Cornell Center  950 Park Avenue, New York, NY 10028, USA | NA |
| Western Institutional Review Board | Houston Institute for Clinical Research  7777 Southwest Freeway, Suite 720, Houston, TX 77074, USA | 28 September 1999  20 April 1999 |
| Western Institutional Review Board | Boulder Medical Center  2750 Broadway, Boulder, CO 80304, USA | 4 October 1999  20 April 1999 |
| IntegReview Ethical Review Board | Center for Clinical Research – Austin  12221 North MoPac Expressway, Austin, Texas 78758, USA  Austin Diagnostic Clinic  12221 North MoPac Expressway, Austin, Texas 78758, USA  North Austin Medical Center  12221 North MoPac  Expressway, Austin, Texas  78758, USA | 17 August 1999  14 May 1999  11 May 1999  26 April 1999  19 April 1999  2 February 2000 |
| Women's Hospital of Texas IRB | Women’s Hospital of Texas  7580 Fannin, Suite 305, Houston, Texas 77054, USA | 20 October 2000  21 April 1999 |
| Western Institutional Review Board | Oklahoma Foundation for Digestive Research  711 Stanton L. Boulevard, Suite 619/624, Oklahoma City, OK 73104, USA  Presbyterian Hospital  700 NE 13th Street, Oklahoma City, OK 73104, USA | 4 November 1999  8 April 1999 |
| Western Institutional Review Board | TriCites Medical Research Associates  321 Midway Medical Park, Suite 3, Bristol, TN 37620, USA | 4 October 1999  14 April 1999 |
| Western Institutional Review Board | Wisconsin Center for Advanced Research  2000 E. Layton Ave., Suite 200, Milwaukee, WI 53207, USA  Center for Digestive Health  2801 W. Kinickinnie River Parkway #560, Milwaukee, WI 53215, USA  Gastroenterology Consultants, Ltd.  2901 W. Kinnickinnie River  Parkway Suite 570,  Milwaukee, WI 53215, USA | 12 April 1999  28 April 1999  18 May 1999  13 October 1999 |
| Western Institutional Review Board | R/D Clinical Research Inc.  135 Oyster Creek Drive, Suite W, Lake Jackson, TX 77566, USA  Brazosport Memorial Hospital  100 Medical Drive, Lake Jackson, TX 77566, USA | 5 October 1999  14 April 1999 |
| Western Institutional Review Board | Nashville Medical Research Institutue, LLC  4230 Harding Road, Suite 309W, Nashville, TN 37205, USA  Nashville Medical Research Institute, LLC  2010 Church Street, Suite 420, Nashville, TN 37205, USA  Nashville Medical Research Institute, LLC  397 Wallace Road, Building C, Suite 407, Nashville, TN 32705, USA | 27 October 1999  5 April 1999 |
| Western Institutional Review Board | Lynn Health Science Institute  5300 N. Independence, Suite 130, Oklahoma City, OK  73112, USA  608 NW 9th, Suite 6110, Oklahoma City, OK 73101, USA | 26 October 1999  4 August 1999  19 April 1999 |
| UC Davis Human Subjects Review Committee | UC Davis General Medicine Research Group  2000 Stockton Blvd., Sacramento, CA 95817, USA  UC Davis Medical Center Division of General Medicine  221 Stockton Blvd., Room PCC 3107, Sacramento, CA 95817, USA | 20 October 1999  18 August 1999 |
| Nalle Clinic Institutional Review Board | Nalle Clinic  1918 Randolph Road, Charlotte, NC 28207, USA | 20 December 1999  11 May 1999  5 April 1999  15 April 1999 |
| Western Institutional Review Board | Miami Research Associates, Inc.  7500 SW 87 Avenue, Suite 202, Miami, FL 33173–5426, USA  Gastroenterology Care Center  7500 SW 87 Avenue, Suite 200, Miami, FL 33173, USA  Ambulatory Surgical Center  8700 Kendall Drive, Suite 100, Miami, FL 33176, USA | 4 May 1999  5 April 1999 |
| Western Institutional Review Board | 13303 Tesson Ferry Road, Suite 35, St. Louis, Missouri 63011, USA | 12 October 1999  4 May 1999  12 April 1999 |
| Western Institutional Review Board | Drug Research Services, Inc.  4720 South I-10 Service Road, Suite 501, Metairie, LA 70001, USA  Lakeside Hospital  4700 South I-10 Service Road, Metairie, LA 70001, USA | 24 November 1999  11 May 1999 |
| Methodist Hospital IRB | Colon and Rectal Surgery, Inc.  8712 W. Dodge Road, Suite 240, Omaha, NE 68114, USA | NA |
| University of Pittsburgh lRB | University of Pittsburgh  Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213, USA | 24 June 1999 |
| PRU-NED-2  (Not registered) | Subcommissie voor de ethiek van het mensgebonden onderzoek | Academisch Ziekenhuis Vrije Universiteit De Boelelaan 1117  1081 HV, Amsterdam, the Netherlands | 25 April 1996 |
| PRU-NED-13  (Not registered) | Medisch Ethische Toetsinscommissie | Site #1  Universitair Medisch Centrum  Heidelberglaan 100, 3584 CX Utrecht, the Netherlands | 15 December 1998 |

aFurther IRB information is not available for this study.

IRB, institutional review board; NA, not available.

**Supplementary references**

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