MYLAN EXHIBIT - 1004 (Part 2) Pg.233
Mylan Pharmaceuticals, Inc. v. Bausch Health Ireland, Ltd. - IPR2022-00722

GenCore version 5.1.6
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OM protein - nucleic search, using frame_plus_p2n model

Run on: August 28, 2005, 09:48:36 ; Search time 2602 Seconds
(without alignments)
297.957 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Xgapop 10.0 , Xgapext 0.5
Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 4708233 seqs, 24227607955 residues

Total number of hits satisfying chosen parameters: 9416466

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Command line parameters:
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-UNITS=bits -START=1 -END=-1 -MATRIX=blosum62 -TRANS=human40.cdi -LIST=45
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Database : GenEmbl:*
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2: gb_htg:*
3: gb_in:*
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14: gb_vi:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	72	6	A79703	A79703 Sequence 37
2	92	96.8	336	6	A79702	A79702 Sequence 36
3	92	96.8	414	9	BC069301	BC069301 Homo sapi
4	92	96.8	583	6	A60251	A60251 Sequence 3
5	92	96.8	583	6	A79701	A79701 Sequence 35
6	92	96.8	583	9	HSGCAPII	Z50753 H.sapiens m
7	92	96.8	596	9	HSU34279	U34279 Human urogu
8	92	96.8	597	6	CQ720645	CQ720645 Sequence
9	92	96.8	3371	9	HSU55058	U55058 Human urogu
10	92	96.8	3600	9	HSGCAP2	Z70295 H.sapiens G
11	92	96.8	141677	9	AC114492	AC114492 Homo sapi
12	90	94.7	522	10	CPUGUMRNA	Z74738 C.porcellus
13	84	88.4	358	10	AF469496	AF469496 Notomys a
14	84	88.4	526	10	RNU41322	U41322 Rattus norv
15	84	88.4	548	10	RNU73898	U73898 Rattus norv
16	84	88.4	554	10	MMU67800	U67800 Mus musculu
17	84	88.4	590	10	MMU90727	U90727 Mus musculu
18	84	88.4	605	10	BC024373	BC024373 Mus muscu
19	84	88.4	651	6	AX402024	AX402024 Sequence
20	84	88.4	651	10	RNU75186	U75186 Rattus norv
21	84	88.4	3703	10	AF006668	AF006668 Mus muscu
22	84	88.4	7274	10	MMU95182	U95182 Mus musculu
23	84	88.4	214456	10	AL645563	AL645563 Mouse DNA
c 24	84	88.4	217927	2	AL606911	AL606911 Mus muscu
c 25	84	88.4	232814	2	BX324150	BX324150 Mus muscu
c 26	84	88.4	243164	2	AC132173	AC132173 Rattus no
27	84	88.4	253902	2	AC095908	AC095908 Rattus no
28	82	86.3	472	4	SDGCAPII	Z83746 S.domestica
29	77	81.1	1003	4	DVU49353	U49353 Didelphis v
30	73	76.8	920	5	AB080642	AB080642 Anguilla
31	73	76.8	941	5	AAN301672	AJ301672 Anguilla
32	73	76.8	1037	5	AAN301673	AJ301673 Anguilla
33	73	76.8	194209	5	BX248318	BX248318 Zebrafish
34	67	70.5	1009	5	AB080640	AB080640 Anguilla
35	64	67.4	433	1	AF302048	AF302048 Vibrio mi
36	63	66.3	62	6	AX252197	AX252197 Sequence
37	63	66.3	65	6	AX252193	AX252193 Sequence
c 38	63	66.3	66	6	AX252196	AX252196 Sequence
c 39	63	66.3	68	6	AX252192	AX252192 Sequence
40	63	66.3	69	6	AX252185	AX252185 Sequence
c 41	63	66.3	69	6	AX252188	AX252188 Sequence
42	63	66.3	69	6	AX252189	AX252189 Sequence
c 43	63	66.3	72	6	AX252182	AX252182 Sequence
44	63	66.3	72	6	AX252183	AX252183 Sequence
c 45	63	66.3	73	6	AX252184	AX252184 Sequence

ALIGNMENTS

RESULT 1
A79703
LOCUS A79703 72 bp DNA linear PAT 20-OCT-1999
DEFINITION Sequence 37 from Patent WO9720049.
ACCESSION A79703
VERSION A79703.1 GI:6092631
KEYWORDS .
SOURCE unidentified
ORGANISM unidentified
unclassified.
REFERENCE 1 (bases 1 to 72)
AUTHORS Forssmann,W. and Kist,A.
TITLE HUMAN PEPTIDE CIRCULATING IN THE BLOOD AND POSSESSING INSULINOTROPIC PROPERTIES
JOURNAL Patent: WO 9720049-A 37 05-JUN-1997;
FORSSMANN WOLF GEORG (DE); KIST ANDREAS (DE)
FEATURES Location/Qualifiers
source 1. .72
/organism="unidentified"
/mol_type="unassigned DNA"
/db_xref="taxon:32644"
ORIGIN

Alignment Scores:
Pred. No.: 1.05e-06 Length: 72
Score: 92.00 Matches: 15
Percent Similarity: 100.00% Conservative: 1
Best Local Similarity: 93.75% Mismatches: 0

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Query Match:            96.84%      Indels:        0
DB:                     6           Gaps:          0

US-10-107-814-20 (1-16) x A79703 (1-72)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db         25 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 72

RESULT 2
A79702
LOCUS       A79702                   336 bp    DNA     linear   PAT 20-OCT-1999
DEFINITION  Sequence 36 from Patent WO9720049.
ACCESSION   A79702
VERSION     A79702.1  GI:6092630
KEYWORDS    .
SOURCE      unidentified
  ORGANISM  unidentified
            unclassified.
REFERENCE   1  (bases 1 to 336)
  AUTHORS   Forssmann,W. and Kist,A.
  TITLE     HUMAN PEPTIDE CIRCULATING IN THE BLOOD AND POSSESSING
            INSULINOTROPIC PROPERTIES
  JOURNAL   Patent: WO 9720049-A 36 05-JUN-1997;
            FORSSMANN WOLF GEORG (DE); KIST ANDREAS (DE)
FEATURES             Location/Qualifiers
     source          1. .336
                     /organism="unidentified"
                     /mol_type="unassigned DNA"
                     /db_xref="taxon:32644"
ORIGIN

Alignment Scores:
Pred. No.:              4.71e-06    Length:        336
Score:                  92.00       Matches:       15
Percent Similarity:     100.00%     Conservative:  1
Best Local Similarity:  93.75%      Mismatches:    0
Query Match:            96.84%      Indels:        0
DB:                     6           Gaps:          0

US-10-107-814-20 (1-16) x A79702 (1-336)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        289 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 336

RESULT 3
BC069301
LOCUS       BC069301                 414 bp    mRNA    linear   PRI 30-JUN-2004
DEFINITION  Homo sapiens guanylate cyclase activator 2B (uroguanylin), mRNA
            (cDNA clone MGC:97480 IMAGE:7262756), complete cds.
ACCESSION   BC069301
VERSION     BC069301.1  GI:47481402
KEYWORDS    MGC.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 414)
  AUTHORS   Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G.,
            Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D.,
            Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K.,
            Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F.,
            Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L.,
            Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L.,
            Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S.,
            Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J.,
            Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J.,
            McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S.,
            Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W.,
            Villalon,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A.,
            Fahey,J., Helton,E., Ketteman,M., Madan,A., Rodrigues,S.,
            Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,
            Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D.,
            Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M.,
            Butterfield,Y.S., Krzywinski,M.I., Skalska,U., Smailus,D.E.,
            Schnerch,A., Schein,J.E., Jones,S.J. and Marra,M.A.
  TITLE     Generation and initial analysis of more than 15,000 full-length
            human and mouse cDNA sequences
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
  PUBMED    12477932
REFERENCE   2  (bases 1 to 414)
  AUTHORS   Strausberg,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (29-APR-2004) National Institutes of Health, Mammalian
            Gene Collection (MGC), Cancer Genomics Office, National Cancer
            Institute, 31 Center Drive, Room 11A03, Bethesda, MD 20892-2590,
            USA
  REMARK    NIH-MGC Project URL: http://mgc.nci.nih.gov
COMMENT     Contact: MGC help desk
            Email: cgapbs-r@mail.nih.gov
            Tissue Procurement: Baylor Human Genome Sequencing Center
            cDNA Library Preparation: Baylor Human Genome Sequencing Center
            cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)
            DNA Sequencing by: Baylor College of Medicine Human Genome
            Sequencing Center
            Center code: BCM-HGSC
            Web site: http://www.hgsc.bcm.tmc.edu/cdna/
            Contact: amg@bcm.tmc.edu
            Gunaratne, P.H., Garcia, A.M., Lu, X., Hulyk, S.W., Loulseged, H.,
            Kowis, C.R., Sneed, A.J., Martin, R.G., Muzny, D.M., Nanavati,
            A.N., Gibbs, R.A.

            Clone distribution: MGC clone distribution information can be found
            through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
            Series: IRBR Plate: 7 Row: h Column: 6.
FEATURES             Location/Qualifiers
     source          1. .414
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /clone="MGC:97480 IMAGE:7262756"
                     /tissue_type="PCR rescued clones"
                     /clone_lib="NIH_MGC_244"
                     /note="Vector: pPCR-Script Amp SK(+)"
     gene            1. .414
                     /gene="GUCA2B"
                     /note="synonyms: GCAP-II, UGN"
                     /db_xref="LocusID:2981"
                     /db_xref="MIM:601271"
     CDS             29. .367
                     /gene="GUCA2B"
                     /codon_start=1
                     /product="guanylate cyclase activator 2B (uroguanylin)"
                     /protein_id="AAH69301.1"
                     /db_xref="GI:47481403"
                     /db_xref="LocusID:2981"
                     /db_xref="MIM:601271"
                     /translation="MGCRAASGLLPGVAVVLLLLLQSTQSVYIQYQGFRVQLESMKKL
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ORIGIN

Alignment Scores:
Pred. No.:              5.77e-06    Length:        414
Score:                  92.00       Matches:       15
Percent Similarity:     100.00%     Conservative:  1
Best Local Similarity:  93.75%      Mismatches:    0
Query Match:            96.84%      Indels:        0
DB:                     9           Gaps:          0

US-10-107-814-20 (1-16) x BC069301 (1-414)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
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Db        317 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 364
```

```
RESULT 4
A60251
LOCUS       A60251                  583 bp    DNA     linear   PAT 06-MAR-1998
DEFINITION  Sequence 3 from Patent WO9706258.
ACCESSION   A60251
VERSION     A60251.1  GI:3715256
KEYWORDS    .
SOURCE      unidentified
  ORGANISM  unidentified
            unclassified.
REFERENCE   1
  AUTHORS   Forssmann,W., Hill,O., Hess,R., Adermann,K., Raida,M., Maegert,H.,
            Meyer,M. and Schulz-Knappe,P.
  TITLE     cDNA SEQUENCE, AMINO-ACID SEQUENCE, DERIVED FROM THE cDNA SEQUENCE,
            OF THE PRECURSOR PROTEIN OF HUMAN GCAP-II/UROGUANYLINE, AND
            AMINO-ACID SEQUENCE OF THE FRAGMENT CIRCULATING IN HUMAN BLOOD
  JOURNAL   Patent: WO 9706258-A 3 20-FEB-1997;
            FORSSMANN WOLF GEORG (DE)
COMMENT     Other publication DE 19528544 970206.
FEATURES             Location/Qualifiers
     source          1. .583
                     /organism="unidentified"
                     /mol_type="unassigned DNA"
                     /db_xref="taxon:32644"
ORIGIN

Alignment Scores:
Pred. No.:              8.07e-06        Length:         583
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     6               Gaps:           0

US-10-107-814-20 (1-16) x A60251 (1-583)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        310 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 357

RESULT 5
A79701
LOCUS       A79701                  583 bp    DNA     linear   PAT 20-OCT-1999
DEFINITION  Sequence 35 from Patent WO9720049.
ACCESSION   A79701
VERSION     A79701.1  GI:6092629
KEYWORDS    .
SOURCE      unidentified
  ORGANISM  unidentified
            unclassified.
REFERENCE   1  (bases 1 to 583)
  AUTHORS   Forssmann,W. and Kist,A.
  TITLE     HUMAN PEPTIDE CIRCULATING IN THE BLOOD AND POSSESSING
            INSULINOTROPIC PROPERTIES
  JOURNAL   Patent: WO 9720049-A 35 05-JUN-1997;
            FORSSMANN WOLF GEORG (DE); KIST ANDREAS (DE)
FEATURES             Location/Qualifiers
     source          1. .583
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                     /mol_type="unassigned DNA"
                     /db_xref="taxon:32644"
ORIGIN

Alignment Scores:
Pred. No.:              8.07e-06        Length:         583
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     6               Gaps:           0

US-10-107-814-20 (1-16) x A79701 (1-583)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        310 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 357

RESULT 6
HSGCAPII
LOCUS       HSGCAPII                583 bp    mRNA    linear   PRI 09-SEP-2004
DEFINITION  H.sapiens mRNA for GCAP-II/uroguanylin precursor.
ACCESSION   Z50753
VERSION     Z50753.1  GI:974823
KEYWORDS    GCAP-II; uroguanylin.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 583)
  AUTHORS   Hill,O., Cetin,Y., Cieslak,A., Magert,H.J. and Forssmann,W.G.
  TITLE     A new human guanylate cyclase-activating peptide (GCAP-II,
            uroguanylin): precursor cDNA and colonic expression
  JOURNAL   Biochim. Biophys. Acta 1253 (2), 146-149 (1995)
  MEDLINE   96106424
   PUBMED   8519795
REFERENCE   2  (bases 1 to 583)
  AUTHORS   Hill,O.
  TITLE     Direct Submission
  JOURNAL   Submitted (04-AUG-1995) Oliver Hill, Molecular Biology, Lower
            Saxony Institute for Peptide, Research, Feodor-Lynen-Strasse 31,
            Hannover, Lower Saxon, 30625, Germany
FEATURES             Location/Qualifiers
     source          1. .583
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /clone="pC515, p16R106, p18R106"
                     /tissue_type="colon"
                     /clone_lib="3'-RACE and 5'-RACE PCR products"
                     /dev_stage="adult"
     5'UTR           1. .21
                     /note="determined by consensus rules"
     CDS             22. .360
                     /note="determined by sequence comparison"
                     /codon_start=1
                     /product="GCAP-II/uroguanylin precursor"
                     /protein_id="CAA90629.1"
                     /db_xref="GI:974824"
                     /db_xref="GOA:Q16661"
                     /db_xref="UniProt/Swiss-Prot:Q16661"
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                     /note="determined by consensus rules"
ORIGIN

Alignment Scores:
Pred. No.:              8.07e-06        Length:         583
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     9               Gaps:           0

US-10-107-814-20 (1-16) x HSGCAPII (1-583)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
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Db        310 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 357

RESULT 7
HSU34279
LOCUS       HSU34279                596 bp    mRNA    linear   PRI 28-MAR-1996
```

```
DEFINITION  Human uroguanylin mRNA, complete cds.
ACCESSION   U34279
VERSION     U34279.1  GI:1236798
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 596)
  AUTHORS   Miyazato,M., Nakazato,M., Yamaguchi,H., Date,Y., Kojima,M.,
            Kangawa,K., Matsuo,H. and Matsukura,S.
  TITLE     Cloning and characterization of a cDNA encoding a precursor for
            human uroguanylin
  JOURNAL   Biochem. Biophys. Res. Commun. 219 (2), 644-648 (1996)
  MEDLINE   96193705
   PUBMED   8605041
REFERENCE   2  (bases 1 to 596)
  AUTHORS   Miyazato,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (17-AUG-1995) Mikiya Miyazato, Biochemistry, National
            Cardiovascular Center Research Institute, Fujishirodai, Suita,
            Osaka 565, Japan
FEATURES             Location/Qualifiers
     source          1. .596
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
     CDS             30. .368
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                     /protein_id="AAC50416.1"
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                     /translation="MGCRAASGLLPGVAVVLLLLLQSTQSVYIQYQGFRVQLESMKKL
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ORIGIN

Alignment Scores:
Pred. No.:              8.24e-06        Length:         596
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     9               Gaps:           0

US-10-107-814-20 (1-16) x HSU34279 (1-596)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        318 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 365

RESULT 8
CQ720645
LOCUS       CQ720645                597 bp    DNA     linear   PAT 03-FEB-2004
DEFINITION  Sequence 6579 from Patent WO02068579.
ACCESSION   CQ720645
VERSION     CQ720645.1  GI:42281502
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Venter,C.J., Adams,M.C., Li,P.W. and Myers,E.W.
  TITLE     Kits, such as nucleic acid arrays, comprising a majority of
            humanexons or transcripts, for detecting expression and other uses
            thereof
  JOURNAL   Patent: WO 02068579-A 6579 06-SEP-2002;
            PE Corporation (NY) (US)
FEATURES             Location/Qualifiers
     source          1. .597
                     /organism="Homo sapiens"
                     /mol_type="unassigned DNA"
                     /db_xref="taxon:9606"
ORIGIN

Alignment Scores:
Pred. No.:              8.25e-06        Length:         597
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     6               Gaps:           0

US-10-107-814-20 (1-16) x CQ720645 (1-597)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        319 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 366

RESULT 9
HSU55058
LOCUS       HSU55058                3371 bp    DNA     linear   PRI 06-SEP-1997
DEFINITION  Human uroguanylin gene, complete cds.
ACCESSION   U55058
VERSION     U55058.1  GI:2353685
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3371)
  AUTHORS   Miyazato,M., Nakazato,M., Matsukura,S., Kangawa,K. and Matsuo,H.
  TITLE     Genomic structure and chromosomal localization of human uroguanylin
  JOURNAL   Genomics 43 (3), 359-365 (1997)
  MEDLINE   97422613
   PUBMED   9268639
REFERENCE   2  (bases 1 to 3371)
  AUTHORS   Miyazato,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (16-APR-1996) Biochemistry, National Cardiovascular
            Center Research Institute, Fujishirodai, Suita, Osaka 565, Japan
FEATURES             Location/Qualifiers
     source          1. .3371
                     /organism="Homo sapiens"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:9606"
     CDS             join(792. .881,2021. .2207,2876. .2937)
                     /codon_start=1
                     /product="uroguanylin"
                     /protein_id="AAC51729.1"
                     /db_xref="GI:2353686"
                     /translation="MGCRAASGLLPGVAVVLLLLLQSTQSVYIQYQGFRVQLESMKKL
                     SDLEAQWAPSPRLQAQSLLPAVCHHPALPQDLQPVCASQEASSIFKTLRTIANDDCEL
                     CVNVACTGCL"
ORIGIN

Alignment Scores:
Pred. No.:              4.47e-05        Length:         3371
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     9               Gaps:           0

US-10-107-814-20 (1-16) x HSU55058 (1-3371)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db       2887 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 2934

RESULT 10
HSGCAP2
LOCUS       HSGCAP2                 3600 bp    DNA     linear   PRI 17-AUG-1996
DEFINITION  H.sapiens GCAP-II gene.
ACCESSION   Z70295
```

```
VERSION     Z70295.1  GI:1495450
KEYWORDS    GCAP-II; guanylyl cyclase; uroguanylin.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3600)
  AUTHORS   Maegert,H.J., Hill,O. and Forssmann,W.G.
  TITLE     Structure of the human uroguanylin / GCAP-II gene and expression
            within the gastrointestinal tract
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 3600)
  AUTHORS   Pardigol,A.
  TITLE     Direct Submission
  JOURNAL   Submitted (25-MAR-1996) Andreas Pardigol, IV - Molecular Biology,
            Lower Saxony Institute for Peptide Research, Feodor-Lynen-Strasse
            31, Hannover, Lower Saxony, 30625, Germany
FEATURES             Location/Qualifiers
     source          1. .3600
                     /organism="Homo sapiens"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:9606"
                     /sex="male"
                     /tissue_type="placenta"
                     /clone_lib="lambda FIX II, Stratagene, Cat. No. 9462039"
     TATA_signal     950. .954
     exon            979. .1110
                     /number=1
     5'UTR           979. .1020
                     /evidence=experimental
     gene            join(1021. .1110,2251. .2437,3106. .3167)
                     /gene="GCAP-II"
     CDS             join(1021. .1110,2251. .2437,3106. .3167)
                     /gene="GCAP-II"
                     /codon_start=1
                     /product="uroguanylin"
                     /protein_id="CAA94311.1"
                     /db_xref="GI:1495451"
                     /db_xref="GOA:Q16661"
                     /db_xref="UniProt/Swiss-Prot:Q16661"
                     /translation="MGCRAASGLLPGVAVVLLLLLQSTQSVYIQYQGFRVQLESMKKL
                     SDLEAQWAPSPRLQAQSLLPAVCHHPALPQDLQPVCASQEASSIFKTLRTIANDDCEL
                     CVNVACTGCL"
     intron          1111. .2250
                     /gene="GCAP-II"
                     /number=1
     exon            2251. .2437
                     /gene="GCAP-II"
                     /number=2
     intron          2438. .3105
                     /gene="GCAP-II"
                     /number=2
     exon            3106. .3390
                     /number=3
     3'UTR           3168. .3390
     polyA_signal    3374. .3379
ORIGIN

Alignment Scores:
Pred. No.:              4.77e-05        Length:         3600
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     9               Gaps:           0

US-10-107-814-20 (1-16) x HSGCAP2 (1-3600)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db       3117 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 3164

RESULT 11
```

```
AC114492
LOCUS       AC114492              141677 bp    DNA     linear   PRI 08-JUL-2003
DEFINITION  Homo sapiens chromosome 1 clone RP11-319C21, complete sequence.
ACCESSION   AC114492 AL354746
VERSION     AC114492.6  GI:32469525
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Zhou,Y., James,R.A., Rouse,G., Wu,Z.,
            Saenphimmachak,C., Buckley,D., Kibukawa,M., Raymond,C. and
            Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Raymond,C. and Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (09-MAR-2002) Genome Center, University of Washington,
            Box 352145, Seattle, WA 98195, USA
REFERENCE   3  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Zhou,Y., James,R.A., Rouse,G., Wu,Z.,
            Saenphimmachak,C., Phelps,K.A., Buckley,D., Raymond,C. and
            Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (24-MAY-2002) Genome Center, University of Washington,
            Box 352145, Seattle, WA 98195, USA
REFERENCE   4  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Zhou,Y., James,R.A., Rouse,G., Wu,Z.,
            Saenphimmachak,C., Buckley,D., Kibukawa,M., Raymond,C. and
            Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-DEC-2002) Genome Center, University of Washington,
            Box 352145, Seattle, WA 98195, USA
REFERENCE   5  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Zhou,Y., James,R.A., Rouse,G., Wu,Z.,
            Saenphimmachak,C., Buckley,D., Kibukawa,M., Raymond,C. and
            Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (25-MAR-2003) Genome Center, University of Washington,
            Box 352145, Seattle, WA 98195, USA
REFERENCE   6  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Zhou,Y., James,R.A., Rouse,G., Wu,Z.,
            Saenphimmachak,C., Buckley,D., Kibukawa,M., Raymond,C. and
            Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (06-JUN-2003) Genome Center, University of Washington,
            Box 352145, Seattle, WA 98195, USA
REFERENCE   7  (bases 1 to 141677)
  AUTHORS   Kaul,R.K., Olson,M.V., Zhou,Y., James,R.A., Rouse,G., Wu,Z.,
            Saenphimmachak,C., Buckley,D., Kibukawa,M., Raymond,C. and
            Haugen,E.D.
  TITLE     Direct Submission
  JOURNAL   Submitted (08-JUL-2003) Genome Center, University of Washington,
            Box 352145, Seattle, WA 98195, USA
COMMENT     On Jul 8, 2003 this sequence version replaced gi:31442465.
            -------------- Genome Center
                Center: University of Washington Genome Center
                Center Code: UWGC
                Web site: http://www.genome.washington.edu
                Contact: uwgchtgs@u.washington.edu
                Drafting Center: SC
            -------------- Project Information
                Center project name: chr-1
                Center clone name: RP11-319C21 (sc0662)
            ------------- Summary Statistics
                Sequencing vector: plasmid; 45% of reads
                Sequencing vector: plasmid; L08752; 55% of reads
                Chemistry: Dye-terminator ET; 88% of reads
                Chemistry: Dye-terminator Big Dye; 12% of reads
                Assembly program: Phrap; version 0.990319
                Consensus quality: 141496 bases at least Q40
```

Consensus quality: 141630 bases at least Q30
Consensus quality: 141668 bases at least Q20
Insert size: 141677; sum-of-contigs
Quality coverage: 9.3x in Q20 bases; sum-of-contigs

Overlapping Sequences:
5': RP1-21K4 (UWGC:sc0801) AL158216, 2000-bp overlap
3': RP11-223A3 (UWGC:sc0655) AC096540, 3338-bp overlap

Note: This is a partial submission. The full clone overlaps are not included.

Sequence Quality Assessment:
This entry has been annotated with sequence quality estimates computed by the Phrap assembly program.
All manually edited bases have been reduced to quality zero.
Quality levels above 40 are expected to have less than 1 error in 10,000 bp.
Base-by-base quality values are not generally visible from the GenBank flat file format but are available as part of this entry's ASN.1 file.

This sequence was finished as follows unless otherwise noted: all regions were either double-stranded or sequenced with an alternate chemistry or covered by high quality data (i.e., Phred quality >= 30); an attempt was made to resolve all sequencing problems, such as compressions and repeats; all regions were covered by at least one plasmid subclone or more than one M13 subclone; and the assembly was confirmed by restriction digest.

Sequence Validation:
This sequence has been validated by Multiple Complete Digest fingerprinting. Comparison of the experimentally derived digest fragments with sequence-predicted fragments is given below. The electronically-digested sequence consists of both insert and vector, in order to accurately represent the entire circular BAC. Small fragments below a variable cutoff (approximately 400-800 bp) are not resolved in the fingerprint and hence do not appear in the table. There are no significant remaining discrepancies between the experimental and predicted values. Uniquely ordered fragments are separated by dashed lines.

EcoRI		HindIII		BglII	
SeqDerMap	FngrPrnt	SeqDerMap	FngrPrnt	SeqDerMap	FngrPrnt
8696	8644	572	<800	7263	7135
6	<800	6382	6726	2067	2064
6233	6558	512	<800	10078	9781
1616	1571	449	<800	1077	1068
5787	5705	1126	1124	6457	6851
7805	7633	1797	1752	4061	4075
2090	2060	782	802	1766	1733
66	<800	13240	13376	187	<800
331	<800	1585	1594	1630	1733
3753	3981	12455	11592	14987	15497
8170	7633	7907	7931	2374	2336
2444	2385	1258	1253	3718	3722
35	<800	1205	1253	4606	4503
2967	2951	9282	9448	1480	1458
16318	16844	462	<800	2143	2064
4023	3981	789	802	6766	6851
1588	1571	1145	1149	9411	9288
704	<800	1364	1390	1397	1362
2407	2385	7487	7407	2378	2336
3412	3507	2061	2093	3057	3095
139	<800	295	<800	2604	2599
525	<800	9993	10285	602	<800
10774	10397	372	<800	1126	1068
1301	1313	1912	1907	511	<800
255	<800	2930	2959	771	<800
57	<800	13235	12794	1475	1458
3067	3084	2698	2779	3206	3253
1372	1313	3327	3389	449	<800
3141	3289	7781	7407	12380	12227
2047	2060	1288	1253	12280	12227
2025	2060	11650	11592	8043	8234
30	<800	5504	5519	709	<800
5956	5964	3812	3875	338	<800
4145	4126	4434	4389	9840	9781
209	<800	133	<800	9730	9781
2316	2274	8006	7931	112	<800
5662	5705	1632	1594	462	<800
1834	1863	2949	2959	7129	7135
4388	4278	6007	5884	9896	9781
1485	1475	2919	2959	3699	3722
1084	1087	3926	3875	5782	5784

Alignment Scores:

Pred. No.:	0.00172	Length:	141677
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	9	Gaps:	0

US-10-107-814-20 (1-16) x AC114492 (1-141677)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db      92768 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 92815
```

RESULT 12
CPUGUMRNA
LOCUS CPUGUMRNA 522 bp mRNA linear ROD 17-AUG-1996

```
DEFINITION  C.porcellus mRNa for uroguanylin.
ACCESSION   Z74738
VERSION     Z74738.1  GI:1495360
KEYWORDS    uroguanylin.
SOURCE      Cavia porcellus (domestic guinea pig)
  ORGANISM  Cavia porcellus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Hystricognathi; Caviidae; Cavia.
REFERENCE   1  (bases 1 to 522)
  AUTHORS   Kruhoeffer,M., Meyer,M.F., Schlatter,E., Kaempf,U., Cetin,Y. and
            Forssmann,W.
  TITLE     Uroguanylin: cGMP signalling in guinea pig kidney
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 522)
  AUTHORS   Kruhoeffer,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (21-JUN-1996) Mogens Kruhoeffer, Molecular Biology, Lower
            Saxony Institute for Peptide Research (IPF), Feodor-Lynen-Strasse
            31, Hannover, 30625, Germany
FEATURES             Location/Qualifiers
     source          1. .522
                     /organism="Cavia porcellus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10141"
                     /tissue_type="stomack"
                     /dev_stage="adult"
     5'UTR           1. .40
     CDS             41. .376
                     /codon_start=1
                     /product="uroguanylin"
                     /protein_id="CAA98994.1"
                     /db_xref="GI:1495361"
                     /db_xref="GOA:P70107"
                     /db_xref="UniProt/Swiss-Prot:P70107"
                     /translation="MGSRTLLGHLSVLAVVLLLLLQGTQSVDIKYQGYQVQLESVKKL
                     KALEEQWVSSPRLQAQDPQPAVCHHPALPLDLQPICTSQEAASILQALRTMDNDECEL
                     CVNIACTGC"
     3'UTR           377. .522
     polyA_signal    505. .510
     polyA_site      522
ORIGIN

Alignment Scores:
Pred. No.:              1.55e-05        Length:         522
Score:                  90.00           Matches:        14
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.33%          Mismatches:     0
Query Match:            94.74%          Indels:         0
DB:                     10              Gaps:           0

US-10-107-814-20 (1-16) x CPUGUMRNA (1-522)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              |||||||||||||||||||||||||:::|||||||||||||||||
Db        329 AACGACGAGTGTGAGCTGTGTGTGAACATCGCCTGTACCGGCTGC 373

RESULT 13
AF469496
LOCUS       AF469496                358 bp    mRNA    linear   ROD 13-FEB-2002
DEFINITION  Notomys alexis uroguanylin mRNA, complete cds.
ACCESSION   AF469496
VERSION     AF469496.1  GI:18653396
KEYWORDS    .
SOURCE      Notomys alexis (Spinifex hopping mouse)
  ORGANISM  Notomys alexis
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae;
            Notomys.
REFERENCE   1  (bases 1 to 358)
  AUTHORS   Donald,J.A. and Bartolo,R.C.
  TITLE     Cloning and expression of guanylin and uroguanylin in the Spinifex
            hopping mouse, Notomys alexis
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 358)
  AUTHORS   Donald,J.A. and Bartolo,R.C.
  TITLE     Direct Submission
  JOURNAL   Submitted (13-JAN-2002) Biological and Chemical Sciences, Deakin
            University, Geelong, Victoria 3217, Australia
FEATURES             Location/Qualifiers
     source          1. .358
                     /organism="Notomys alexis"
                     /mol_type="mRNA"
                     /db_xref="taxon:184396"
     CDS             29. .352
                     /codon_start=1
                     /product="uroguanylin"
                     /protein_id="AAL77417.1"
                     /db_xref="GI:18653397"
                     /translation="MSGSQLWAAVVVLLLLQSAQGVYIKYHGFQVQLESVKKLSELEE
                     KQMSSPQLRKSGLLLPDVCHNPALPLDLQPICASQEAASTFKALRTIATDECELCINV
                     ACTGC"
ORIGIN

Alignment Scores:
Pred. No.:              0.000106        Length:         358
Score:                  84.00           Matches:        13
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  92.86%          Mismatches:     0
Query Match:            88.42%          Indels:         0
DB:                     10              Gaps:           0

US-10-107-814-20 (1-16) x AF469496 (1-358)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||||:::||||||||||||||||||||
Db        308 GACGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 349

RESULT 14
RNU41322
LOCUS       RNU41322                526 bp    mRNA    linear   ROD 13-DEC-2001
DEFINITION  Rattus norvegicus uroguanylin mRNA, complete cds.
ACCESSION   U41322
VERSION     U41322.1  GI:1667397
KEYWORDS    .
SOURCE      Rattus norvegicus (Norway rat)
  ORGANISM  Rattus norvegicus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae;
            Rattus.
REFERENCE   1  (bases 1 to 526)
  AUTHORS   Miyazato,M., Nakazato,M., Matsukura,S., Kangawa,K. and Matsuo,H.
  TITLE     Uroguanylin gene expression in the alimentary tract and
            extra-gastrointestinal tissues
  JOURNAL   FEBS Lett. 398 (2-3), 170-174 (1996)
  MEDLINE   97131589
   PUBMED   8977100
REFERENCE   2  (bases 1 to 526)
  AUTHORS   Miyazato,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (27-NOV-1995) Mikiya Miyazato, Biochemistry, National
            Cardiovascular Center Reserch Institute, Fujishirodai, Suita, Osaka
            565, Japan
FEATURES             Location/Qualifiers
     source          1. .526
                     /organism="Rattus norvegicus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10116"
     CDS             37. .357
                     /codon_start=1
                     /product="uroguanylin"
                     /protein_id="AAB18760.1"
                     /db_xref="GI:1667398"
                     /translation="MSGSQLWAAVLLLLVLQSAQGVYIKYHGFQVQLESVKKLNELEE
                     KQMSDPQQQKSGLLPDVCYNPALPLDLQPVCASQEAASTFKALRTIATDECELCINVA
                     CTGC"
ORIGIN
```

```
Alignment Scores:
Pred. No.:              0.000154        Length:         526
Score:                  84.00           Matches:        13
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  92.86%          Mismatches:     0
Query Match:            88.42%          Indels:         0
DB:                     10              Gaps:           0

US-10-107-814-20 (1-16) x RNU41322 (1-526)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              |||||||||||||||||||:::|||||||||||||||||||||
Db        313 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 354

RESULT 15
RNU73898
LOCUS       RNU73898                548 bp    mRNA    linear   ROD 05-NOV-1996
DEFINITION  Rattus norvegicus preprouroguanylin mRNA, complete cds.
ACCESSION   U73898
VERSION     U73898.1  GI:1658404
KEYWORDS    .
SOURCE      Rattus norvegicus (Norway rat)
  ORGANISM  Rattus norvegicus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae;
            Rattus.
REFERENCE   1  (bases 1 to 548)
  AUTHORS   Li,Z., Perkins,A.G., Peters,M.F., Campa,M.J. and Goy,M.F.
  TITLE     Purification, cDNA sequence, and tissue distribution of rat
            uroguanylin
  JOURNAL   Regul. Pept. (1996) In press
REFERENCE   2  (bases 1 to 548)
  AUTHORS   Li,Z., Perkins,A.G. and Goy,M.F.
  TITLE     Direct Submission
  JOURNAL   Submitted (10-OCT-1996) Physiology, UNC-CH, Room 68, M.S.R.B., CB
            #7545, Chapel Hill, NC 27599, USA
FEATURES             Location/Qualifiers
     source          1. .548
                     /organism="Rattus norvegicus"
                     /mol_type="mRNA"
                     /strain="Sprague-Dawley"
                     /db_xref="taxon:10116"
     CDS             53. .373
                     /function="activates cyclic GMP synthesis and regulates
                     transepithelial ion fluxes"
                     /note="signaling peptide; intestinal peptide."
                     /codon_start=1
                     /product="preprouroguanylin"
                     /protein_id="AAB18331.1"
                     /db_xref="GI:1658405"
                     /translation="MSGSQLWAAVLLLLVLQSAQGVYIKYHGFQVQLESVKKLNELEE
                     KQMSDPQQQKSGLLPDVCYNPALPLDLQPVCASQEAASTFKALRTIATDECELCINVA
                     CTGC"
ORIGIN

Alignment Scores:
Pred. No.:              0.000161        Length:         548
Score:                  84.00           Matches:        13
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  92.86%          Mismatches:     0
Query Match:            88.42%          Indels:         0
DB:                     10              Gaps:           0

US-10-107-814-20 (1-16) x RNU73898 (1-548)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              |||||||||||||||||||:::|||||||||||||||||||||
Db        329 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 370


Search completed: August 28, 2005, 13:33:41
Job time : 2614 secs
```

GenCore version 5.1.6
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OM protein - nucleic search, using frame_plus_p2n model

Run on: August 28, 2005, 06:39:36 ; Search time 361 Seconds
(without alignments)
262.371 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Xgapop 10.0 , Xgapext 0.5
Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 4390206 seqs, 2959870667 residues

Total number of hits satisfying chosen parameters: 8780412

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Command line parameters:
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-Q=/cgn2_1/USPTO_spool/US10107814/runat_26082005_122650_15698/app_query.fasta_1.199
-DB=N_Geneseq_16Dec04 -QFMT=fastap -SUFFIX=p2n.rng -MINMATCH=0.1 -LOOPCL=0
-LOOPEXT=0 -UNITS=bits -START=1 -END=-1 -MATRIX=blosum62 -TRANS=human40.cdi
-LIST=45 -DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100 -THR_MIN=0 -ALIGN=15
-MODE=LOCAL -OUTFMT=pto -NORM=ext -HEAPSIZE=500 -MINLEN=0 -MAXLEN=2000000000
-USER=US10107814_@CGN_1_1_644_@runat_26082005_122650_15698 -NCPU=6 -ICPU=3
-NO_MMAP -LARGEQUERY -NEG_SCORES=0 -WAIT -DSPBLOCK=100 -LONGLOG
-DEV_TIMEOUT=120 -WARN_TIMEOUT=30 -THREADS=1 -XGAPOP=10 -XGAPEXT=0.5 -FGAPOP=6
-FGAPEXT=7 -YGAPOP=10 -YGAPEXT=0.5 -DELOP=6 -DELEXT=7

Database : N_Geneseq_16Dec04:*
1: geneseqn1980s:*
2: geneseqn1990s:*
3: geneseqn2000s:*
4: geneseqn2001as:*
5: geneseqn2001bs:*
6: geneseqn2002as:*
7: geneseqn2002bs:*
8: geneseqn2003as:*
9: geneseqn2003bs:*
10: geneseqn2003cs:*
11: geneseqn2003ds:*
12: geneseqn2004as:*
13: geneseqn2004bs:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	583	2	AAT65115	Aat65115 Human GCA
2	92	96.8	583	2	AAT60819	Aat60819 Guanylate
3	92	96.8	596	10	ADD29859	Add29859 Human tum
4	84	88.4	651	6	ABK63793	Abk63793 Rat seque
5	84	88.4	651	12	ADP72757	Adp72757 Renal tox
6	63	66.3	62	4	ABA01874	Aba01874 Human the
7	63	66.3	65	4	ABA01870	Aba01870 Human the
c 8	63	66.3	66	4	ABA01873	Aba01873 Human the
9	63	66.3	68	4	ABA01866	Aba01866 Human the
c 10	63	66.3	68	4	ABA01869	Aba01869 Human the
c 11	63	66.3	69	4	ABA01865	Aba01865 Human the
12	63	66.3	69	4	ABA01862	Aba01862 Human the
c 13	63	66.3	69	13	ADR48400	Adr48400 Oligonucl
14	63	66.3	69	13	ADR48399	Adr48399 Oligonucl
15	63	66.3	72	4	ABA01860	Aba01860 Human the
c 16	63	66.3	73	4	ABA01861	Aba01861 Human the
17	63	66.3	236	2	AAQ23866	Aaq23866 Heat-stab
18	63	66.3	433	2	AAQ20050	Aaq20050 Sequence
19	63	66.3	433	2	AAQ89260	Aaq89260 E. coli s
20	63	66.3	950	8	ACC79521	Acc79521 ST gene a
21	63	66.3	1183	8	ACC79524	Acc79524 3' flanki
22	60	63.2	325	8	ACC85777	Acc85777 Human NOV
23	58	61.1	57	2	AAZ07540	Aaz07540 ST recept
24	58	61.1	57	2	AAZ07541	Aaz07541 ST recept
25	58	61.1	57	13	ADR45821	Adr45821 Nucleotid
26	58	61.1	57	13	ADR45824	Adr45824 Nucleotid
27	58	61.1	69	13	ADR48402	Adr48402 Oligonucl
c 28	58	61.1	69	13	ADR48403	Adr48403 Oligonucl
29	58	61.1	243	2	AAQ23865	Aaq23865 Heat-stab
30	57	60.0	69	4	ABA01896	Aba01896 ClpG-STh
31	57	60.0	102	4	ABA01876	Aba01876 Human the
32	56	58.9	65	6	ABN31054	Abn31054 Rat splic
33	56	58.9	367	8	ACC85776	Acc85776 Human NOV
34	56	58.9	367	11	ADJ18913	Adj18913 Human NOV
35	56	58.9	409	8	ACC85775	Acc85775 Human NOV
36	56	58.9	567	10	ABT41905	Abt41905 Toxicity
37	56	58.9	567	12	ADP72737	Adp72737 Renal tox
38	56	58.9	571	6	ABL61837	Abl61837 Colon ade
39	56	58.9	571	10	ADD29595	Add29595 Human tum
40	56	58.9	589	2	AAZ22677	Aaz22677 Human gua
41	56	58.9	649	4	AAH57434	Aah57434 Human int
42	56	58.9	650	10	AAD59154	Aad59154 Human gua
43	56	58.9	655	9	ADA10942	Ada10942 Human cDN
44	56	58.9	655	12	ADG47982	Adg47982 Human gua
45	56	58.9	4595	2	AAT65123	Aat65123 Human GCA

ALIGNMENTS

RESULT 1
AAT65115
ID AAT65115 standard; cDNA; 583 BP.
XX
AC AAT65115;
XX
DT 22-APR-1998 (first entry)
XX
DE Human GCAP-II precursor cDNA.
XX
KW Guanyl cyclase C activating peptide II; GCAP-II; insulinotropic;
KW diabetes; endocrine disorder; diagnosis; treatment; human; ds.
XX
OS Homo sapiens.
XX
FH Key Location/Qualifiers
FT CDS 22. .360
FT /*tag= a
FT /product= "GCAP-II precursor"
XX
PN DE19543628-A1.
XX
PD 28-MAY-1997.
XX
PF 24-NOV-1995; 95DE-01043628.
XX
PR 24-NOV-1995; 95DE-01043628.
XX
PA (FORS/) FORSSMANN W.

```
XX
PI   Forssmann W,  Kist A,  Kruhoeffer M,  Meyer M,  Pardigol A,  Heine G;
XX
DR   WPI; 1997-290350/27.
DR   P-PSDB; AAW18498.
XX
PT   New guanyl cyclase C activating peptide fragments - have insulinotropic
PT   activity, useful for treating diabetes, etc.
XX
PS   Example 6; Fig 11; 33pp; German.
XX
CC   This cDNA sequence encodes a precursor of the guanyl cyclase C activating
CC   peptide, GCAP-II, which affects insulin secretion by the beta cells in
CC   the pancreas. This peptide is useful for treating pancreatic endocrine
CC   disorders, especially diabetes mellitus type II, renal and intestinal
CC   disorders, disorders of the gastrointestinal, respiratory and urogenital
CC   apparatus, disorders of the cardiovascular and nervous systems, disorders
CC   of the integuments and sense organs and diseases associated with GCAP-II
CC   (89-112) deficiency. This peptide can be used for treatment of
CC   electrolyte effects on bone reconstruction (osteoporosis) or the dental
CC   apparatus. Antibodies to GCAP-II (89-112) can be used to treat diseases
CC   associated with overproduction of GCAP-II (89-112). Human GCAP-II (89-
CC   112) and GCAP-I (99-15) cDNA are useful for diagnosis and treatment of
CC   the above disorders e.g. gene therapy for diabetes
XX
SQ   Sequence 583 BP; 115 A; 198 C; 167 G; 103 T; 0 U; 0 Other;

Alignment Scores:
Pred. No.:                9.8e-05        Length:          583
Score:                    92.00          Matches:         15
Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
Query Match:              96.84%         Indels:          0
DB:                       2              Gaps:            0

US-10-107-814-20 (1-16) x AAT65115 (1-583)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        310 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 357

RESULT 2
AAT60819
ID   AAT60819 standard; cDNA; 583 BP.
XX
AC   AAT60819;
XX
DT   29-OCT-1997  (first entry)
XX
DE   Guanylate cyclase activating peptide II cDNA.
XX
KW   Human; guanylate cyclase; activating peptide; GCAP-II; cGMP;
KW   transepithelial transport; treatment; kidney; intestinal; respiratory;
KW   urogenital; circulatory; nervous system; disorder; disease; endocrine;
KW   sensory; system; osteoporosis; dental; pancreas; diabetes; hypophysis;
KW   gastrointestinal tract; diarrhoea; gene therapy; probe;
KW   recombinant production; transgenic animal; antibody; immunoassay reagent;
KW   ss.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   CDS             22. .360
FT                   /*tag=  a
FT   sig_peptide     22. .285
FT                   /*tag=  b
FT   mat_peptide     286. .357
FT                   /*tag=  c
FT                   /product= "guanylate_cyclase_activating_peptide_II"
FT   primer_bind     complement(328. .345)
FT                   /*tag=  d
FT                   /bound_moiety= "primer HUGU-5 (AAT60814)"
FT   primer_bind     complement(346. .366)
FT                   /*tag=  e
FT                   /bound_moiety= "primer HUGU-8 (AAT60816)"
FT   primer_bind     442. .461
FT                   /*tag=  f
FT                   /bound_moiety= "primer HUGU-10 (AAT60818)"
FT   primer_bind     462. .482
FT                   /*tag=  g
FT                   /bound_moiety= "primer HUGU-9 (AAT60817)"
FT   primer_bind     558. .583
FT                   /*tag=  h
FT                   /bound_moiety= "primer HUGU-7 (AAT60815)"
XX
PN   DE19528544-A1.
XX
PD   06-FEB-1997.
XX
PF   03-AUG-1995;   95DE-01028544.
XX
PR   03-AUG-1995;   95DE-01028544.
XX
PA   (FORS/) FORSSMANN W.
XX
PI   Forssmann W;
XX
DR   WPI; 1997-110032/11.
DR   P-PSDB; AAW10595.
XX
PT   Guanylate cyclase activating peptide II - increases cGMP formation, and
PT   controls transport of water and electrolytes across epithelial cells.
XX
PS   Claim 2; Page 4; 15pp; German.
XX
CC   The present sequence encodes the human guanylate cyclase activating
CC   peptide II (GCAP-II), which increases cGMP formation, and is involved in
CC   the control of transepithelial water and electrolyte transport. GCAP-II
CC   can be used to treat a variety of kidney, intestinal, respiratory,
CC   urogenital, circulatory and nervous system disorders, diseases of the
CC   endocrine and sensory systems (e.g. osteoporosis, and dental disease),
CC   disorders of the pancreas (e.g. diabetes, and hypophysis) or the
CC   endocrine gastrointestinal tract and for the long term treatment of
CC   diarrhoea, without inducing an immune response. The GCAP-II cDNA can be
CC   used to treat the same conditions, clone the GCAP-II-encoding gene for
CC   use in gene therapy, as a hybridisation probe and for the production of
CC   recombinant GCAP-II or transgenic animal creation. Antibodies raised
CC   against GCAP-II are useful as immunoassay reagents. GCAP-II is
CC   administered at, e.g. 100-1200 microg/day by intravenous or intramuscular
CC   injection or 300-1200 microg/day subcutaneously. It may also be given
CC   orally, intranasally or by inhalation, in typical unit doses of 0.3-30
CC   mg. GCAP-II was chemically synthesised, or isolated by chromatography
CC   from transformed eukaryotic or prokaryotic cells, or human blood. When
CC   T84 cells were incubated with synthetic GCAP-II, generation of cGMP was
CC   increased in a dose dependent manner. GCAP-II influences cGMP production
CC   via a known receptor for heat stable enterotoxin. Other stomach,
CC   intestinal, pancreatic and liver cells also responded to GCAP-II, e.g.
CC   via changes in intracellular Ca2+ ion concentration
XX
SQ   Sequence 583 BP; 115 A; 198 C; 167 G; 103 T; 0 U; 0 Other;

Alignment Scores:
Pred. No.:                9.8e-05        Length:          583
Score:                    92.00          Matches:         15
Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
Query Match:              96.84%         Indels:          0
DB:                       2              Gaps:            0

US-10-107-814-20 (1-16) x AAT60819 (1-583)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        310 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 357

RESULT 3
```

ADD29859
ID ADD29859 standard; mRNA; 596 BP.
XX
AC ADD29859;
XX
DT 15-JAN-2004 (first entry)
XX
DE Human tumour suppressor mRNA SEQ ID NO:290.
XX
KW ss; human; tumour suppressor; cancer; cancer; cytostatic; gene therapy.
XX
OS Homo sapiens.
XX
PN WO2003058201-A2.
XX
PD 17-JUL-2003.
XX
PF 31-DEC-2002; 2002WO-US041825.
XX
PR 31-DEC-2001; 2001US-0345317P.
XX
PA (QUAR-) QUARK BIOTECH INC.
PA (CLEV-) CLEVELAND CLINIC FOUND.
XX
PI Feinstein E, Gudkov AV;
XX
DR WPI; 2003-598393/56.
XX
PT Diagnosing cancer comprises determining the polypeptide or polynucleotide
PT levels e.g., hepatic lipase, in a sample from a subject, where a higher
PT level compared to that in a subject free of cancer is indicative of
PT cancer.
XX
PS Disclosure; SEQ ID NO 290; 272pp; English.
XX
CC The invention relates to a novel method for diagnosing a cancer in a
CC subject. the method comprises determining, in a sample from the subject,
CC the level of at least one polypeptide, where a higher level of the
CC polypeptide compared to the level of the polypeptide in a subject free of
CC cancer is indicative of cancer. The polypeptide is selected from any of
CC the polypeptides encoded by the polynucleotides listed in the
CC specification and polypeptides which are at least 70% homologous to the
CC polypeptides. The method of the invention has cytostatic activity, and
CC may have a use in gene therapy. The method is useful in identifying
CC markers specific for one or several types of cancer, depending on the
CC tissue origin, which may be used in numerous diagnostic and prognostic
CC applications as well as cancer type-specific targets for therapeutic
CC intervention. The compounds that modulate the activity of a tumour
CC suppressor gene are useful in the treatment of cancer or as anti-cancer
CC drugs. The present sequence represents a polynucleotide of the invention.
XX
SQ Sequence 596 BP; 118 A; 203 C; 172 G; 103 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.000101	Length:	596
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	10	Gaps:	0

US-10-107-814-20 (1-16) x ADD29859 (1-596)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        318 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 365
```

RESULT 4
ABK63793
ID ABK63793 standard; cDNA; 651 BP.
XX
AC ABK63793;
XX
DT 18-JUN-2002 (first entry)
XX
DE Rat sequence differentially expressed in response to a hepatotoxin #1700.
XX
KW Rat; ss; hepatotoxin; expressed sequence tag; EST; drug screening;
KW differential expression; centrilobular necrosis; steatosis.
XX
OS Rattus norvegicus.
XX
PN WO200210453-A2.
XX
PD 07-FEB-2002.
XX
PF 30-JUL-2001; 2001WO-US023872.
XX
PR 31-JUL-2000; 2000US-0222040P.
PR 02-NOV-2000; 2000US-0244880P.
PR 11-MAY-2001; 2001US-0290029P.
PR 15-MAY-2001; 2001US-0290645P.
PR 22-MAY-2001; 2001US-0292336P.
PR 06-JUN-2001; 2001US-0295798P.
PR 13-JUN-2001; 2001US-0297457P.
PR 19-JUN-2001; 2001US-0298884P.
PR 09-JUL-2001; 2001US-0303459P.
XX
PA (GENE-) GENE LOGIC INC.
XX
PI Mendrick D, Porter MW, Johnson KR, Castle AL, Elashoff MR;
XX
DR WPI; 2002-241625/29.
XX
PT Predicting toxic effects of compounds or the progression of these toxic
PT effects by determining the changes in gene expression in tissues or cells
PT exposed to the toxin and comparing these to gene expression in unexposed
PT tissues or cells.
XX
PS Claim 1; SEQ ID NO 1700; 239pp; English.
XX
CC The invention relates to methods for predicting toxic effects of
CC compounds or the progression of these toxic effects by determining the
CC global changes in gene expression in tissues or cells exposed to the
CC toxin and comparing these to gene expression in unexposed tissues or
CC cells. Also included are methods of predicting at least one toxic effect
CC of a compound or progression of a toxic effect, preferably the
CC hepatotoxicity of a compound, comprising detecting the level of
CC expression in a tissue or cell sample exposed to the compound of two or
CC more genes listed in the specification, where differential expression of
CC the genes is indicative of at least one toxic effect or progression. The
CC method can also be used to identify an agent which modulates the toxic
CC response and predict cellular pathways that a compound modulates in a
CC cell. The methods utilise a set of at least two probes (on a solid
CC support in kit form), where each of the probes comprises a sequence that
CC specifically hybridises to a gene listed in the specification, a computer
CC system comprising a database containing information identifying the
CC expression level in a tissue or cell sample exposed to a hepatotoxin of a
CC set of genes comprising at least two genes listed in the specification,
CC and a user interface to view the information used to present information
CC identifying the expression level in a tissue or cell of at least one gene
CC listed in the specification. The method is useful for elucidating global
CC changes in gene expression and for identifying toxicity markers in
CC tissues or cell exposed to a known toxin. The genes may be used as
CC toxicity markers in drug screening and toxicity assays. The genes and
CC gene expression information may be used as diagnostic markers for the
CC prediction or identification of the physiological state of tissue or cell
CC sample that has been exposed to a compound or agent. Hepatotoxicity is
CC characterised by centrilobular necrosis and steatosis. The present
CC sequence is an expressed sequence tag (EST) or cDNA derived from a gene
CC which is differentially expressed in response to a hepatotoxic agent
XX
SQ Sequence 651 BP; 165 A; 185 C; 169 G; 132 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.00178	Length:	651

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Score:                  84.00          Matches:       13
Percent Similarity:     100.00%        Conservative:  1
Best Local Similarity:  92.86%         Mismatches:    0
Query Match:            88.42%         Indels:        0
DB:                     6              Gaps:          0

US-10-107-814-20 (1-16) x ABK63793 (1-651)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||:::||||||||||||||||||||||
Db        440 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 481

RESULT 5
ADP72757
ID   ADP72757 standard; DNA; 651 BP.
XX
AC   ADP72757;
XX
DT   26-AUG-2004  (first entry)
XX
DE   Renal toxin progression gene marker #1346.
XX
KW   ds; toxic effect; gene expression profile; kidney tissue;
KW   differential gene expression; toxicity progression; toxicity marker;
KW   drug screening; toxicity assay; kidney pathology; nephritis;
KW   kidney necrosis; glomerular injury; tubular injury;
KW   focal segmental glomerulosclerosis.
XX
OS   Rattus norvegicus.
XX
PN   WO2004048598-A2.
XX
PD   10-JUN-2004.
XX
PF   24-NOV-2003; 2003WO-US037556.
XX
PR   22-NOV-2002; 2002US-00301856.
XX
PA   (GENE-) GENE LOGIC INC.
XX
PI   Mendrick DL,  Porter MW,  Johnson KR,  Castle A,  Higgs B;
PI   Elashoff M;
XX
DR   WPI; 2004-460771/43.
XX
PT   Predicting (the progression of) a toxic effect of a compound, for
PT   monitoring the progression of renal disease states, comprises preparing a
PT   gene expression profile of a kidney tissue or cell sample exposed to the
PT   compound.
XX
PS   Claim 11; SEQ ID NO 1346; 266pp; English.
XX
CC   The invention relates to a method of predicting (the progression of) a
CC   toxic effect of a compound by preparing a gene expression profile of a
CC   kidney tissue or cell sample exposed to the compound and comparing the
CC   gene expression profile to a database, or detecting the level of gene(s)
CC   expression in a tissue or cell sample exposed to the compound, where
CC   differential gene expression compared to a control indicates a toxic
CC   effect (toxicity progression). The method is useful for predicting (the
CC   progression of) at least one toxic effect of a compound. The genes are
CC   useful as toxicity markers in drug screening and toxicity assays. The
CC   methods are useful for predicting the likelihood that a compound or test
CC   agent will induce various specific kidney pathologies, such as nephritis,
CC   kidney necrosis, glomerular and tubular injury, or focal segmental
CC   glomerulosclerosis. The methods are useful for determining the similarity
CC   of a toxic response to one or more individual compounds and for
CC   predicting or elucidating the potential cellular pathways influenced,
CC   induced or modulated by the compound or test agent. The kit is useful for
CC   predicting or modelling the toxic response of a test compound, for
CC   monitoring the progression of renal disease states, for identifying genes
CC   that show promise as new drug targets and for screening known and newly
CC   designed drugs. This sequence corresponds to a gene marker used in the
CC   method of the invention. (Note: The sequence data for this patent did not
CC   form part of the printed specification, but was obtained in electronic
CC   format directly from WIPO at ftp.wipo.int/pub/published_pct_sequences).
XX
SQ   Sequence 651 BP; 165 A; 185 C; 169 G; 132 T; 0 U; 0 Other;

Alignment Scores:
Pred. No.:              0.00178        Length:        651
Score:                  84.00          Matches:       13
Percent Similarity:     100.00%        Conservative:  1
Best Local Similarity:  92.86%         Mismatches:    0
Query Match:            88.42%         Indels:        0
DB:                     12             Gaps:          0

US-10-107-814-20 (1-16) x ADP72757 (1-651)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||:::||||||||||||||||||||||
Db        440 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 481

RESULT 6
ABA01874
ID   ABA01874 standard; DNA; 62 BP.
XX
AC   ABA01874;
XX
DT   01-FEB-2002  (first entry)
XX
DE   Human thermostable enterotoxin STh coding fragment STNDG1.
XX
KW   Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW   guanyl cyclase-C; GC-C; STa; ds.
XX
OS   Homo sapiens.
XX
PN   FR2805994-A1.
XX
PD   14-SEP-2001.
XX
PF   10-MAR-2000; 2000FR-00003141.
XX
PR   10-MAR-2000; 2000FR-00003141.
XX
PA   (INRG ) INRA INST NAT RECH AGRONOMIQUE.
XX
PI   Der Vartanian M,  Batisson I;
XX
DR   WPI; 2001-640835/74.
XX
PT   New compound for detecting and treating metastatic colorectal cancer
PT   comprises a conjugate of an STa peptide and an immunogenic protein which
PT   binds to the guanyl cyclase-c receptor.
XX
PS   Disclosure; Page 23; 126pp; French.
XX
CC   The present invention relates to a conjugate which comprises an E. coli
CC   thermostable enterotoxin (STa) peptide and an active molecule where the
CC   STa peptide has a conformation such that it is capable of binding to the
CC   guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC   diagnosis and treatment of metastatic colorectal cancer. The present
CC   sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC   sequence
XX
SQ   Sequence 62 BP; 13 A; 12 C; 15 G; 22 T; 0 U; 0 Other;

Alignment Scores:
Pred. No.:              0.174          Length:        62
Score:                  63.00          Matches:       10
Percent Similarity:     83.33%         Conservative:  0
Best Local Similarity:  83.33%         Mismatches:    2
Query Match:            66.32%         Indels:        0
DB:                     4              Gaps:          0

US-10-107-814-20 (1-16) x ABA01874 (1-62)
```

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         18 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 53
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RESULT 7
ABA01870
ID ABA01870 standard; DNA; 65 BP.
XX
AC ABA01870;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragmentr SPGST5.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX
PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX
PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 65 BP; 16 A; 13 C; 12 G; 24 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.183	Length:	65
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	4	Gaps:	0

US-10-107-814-20 (1-16) x ABA01870 (1-65)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         21 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 56
```

RESULT 8
ABA01873/c
ID ABA01873 standard; DNA; 66 BP.
XX
AC ABA01873;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragment STNDG2.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX
PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX
PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 66 BP; 23 A; 16 C; 13 G; 14 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.186	Length:	66
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	4	Gaps:	0

US-10-107-814-20 (1-16) x ABA01873 (1-66)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         45 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 10
```

RESULT 9
ABA01866
ID ABA01866 standard; DNA; 68 BP.
XX
AC ABA01866;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragment Sth69V5.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX

PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX
PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 68 BP; 15 A; 14 C; 16 G; 23 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.193	Length:	68
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	4	Gaps:	0

US-10-107-814-20 (1-16) x ABA01866 (1-68)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         23 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 58
```

RESULT 10
ABA01869/c
ID ABA01869 standard; DNA; 68 BP.
XX
AC ABA01869;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragment SPGST5.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX
PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX
PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 68 BP; 26 A; 12 C; 14 G; 16 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.193	Length:	68
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	4	Gaps:	0

US-10-107-814-20 (1-16) x ABA01869 (1-68)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         45 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 10
```

RESULT 11
ABA01865/c
ID ABA01865 standard; DNA; 69 BP.
XX
AC ABA01865;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragment Sth69V3.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX
PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX
PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 69 BP; 24 A; 16 C; 14 G; 15 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.196	Length:	69
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0

DB: 4 Gaps: 0

US-10-107-814-20 (1-16) x ABA01865 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         50 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 15
```

RESULT 12
ABA01862
ID ABA01862 standard; DNA; 69 BP.
XX
AC ABA01862;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragment Sth69C5.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX
PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX
PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 69 BP; 18 A; 17 C; 14 G; 20 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.196	Length:	69
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	4	Gaps:	0

US-10-107-814-20 (1-16) x ABA01862 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         28 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 63
```

RESULT 13
ADR48400/c
ID ADR48400 standard; DNA; 69 BP.
XX
AC ADR48400;
XX
DT 04-NOV-2004 (first entry)
XX
DE Oligonucleotide MO3622.
XX
KW Gastrointestinal; antiinflammatory; laxative; cardiant; antiulcer;
KW anorectic; cardiovascular; cytostatic; analgesic; CNS; respiratory;
KW neuroprotective; vasotropic; auditory; antiemetic; antiasthmatic;
KW nephrotropic; hepatotropic; virucide; immunosuppressive; antiallergic;
KW antidiabetic; ophthalmological; tranquiliser; hypnotic; nootropic;
KW guanylate cyclase C; GC-C; receptor; gastrointestinal disorder;
KW irritable bowel syndrome; constipation; gastroesophageal reflux disease;
KW heartburn; dyspepsia; gastroparesis; Crohn's disease; ulcerative colitis;
KW inflammatory bowel disease; obesity; heart failure; cystic fibrosis;
KW cancer; respiratory disorder; neurological disorder; carbonate imbalance;
KW erectile dysfunction; inner ear disorder; slow digestion; nausea;
KW vomiting; bloating; asthma; nephritis; hepatitis; pancreatitis; allergy;
KW retinopathy; nephropathy; headache; anxiety; sleep disorder; ds.
XX
OS Unidentified.
XX
PN WO2004069165-A2.
XX
PD 19-AUG-2004.
XX
PF 28-JAN-2004; 2004WO-US002390.
XX
PR 28-JAN-2003; 2003US-0443098P.
PR 15-MAY-2003; 2003US-0471288P.
PR 12-NOV-2003; 2003US-0519460P.
XX
PA (MICR-) MICROBIA INC.
XX
PI Currie MG, Mahajan-Miklos S;
XX
DR WPI; 2004-604332/58.
XX
PT Novel purified peptide capable of activating the guanylate cyclase C
PT receptor, useful for treating obesity, congestive heart failure and
PT benign prostatic hyperplasia.
XX
PS Example 1; Page 39; 93pp; English.
XX
CC The invention relates to a purified peptide (P1) capable of activating
CC the guanylate cyclase C (GC-C) receptor. Further disclosed is a
CC pharmaceutical composition comprising the peptide of the invention. The
CC composition of the invention is useful for treating a gastrointestinal
CC disorder in a patient, which involves administering P1, where the
CC gastrointestinal disorder is gastrointestinal motility disorder,
CC irritable bowel syndrome, chronic constipation, a functional
CC gastrointestinal disorder, gastroesophageal reflux disease, functional
CC heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia,
CC gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-
CC obstruction, Crohn's disease, ulcerative colitis or inflammatory bowel
CC disease. The peptide of the invention is also useful for treating
CC obesity, congestive heart failure, cystic fibrosis or a patient suffering
CC from constipation. The P1/GC-C receptor agonist is useful for treating
CC cancer, respiratory disorder, neurological disorder, disorder associated
CC with carbonate imbalance, erectile dysfunction, insulin-related disorder
CC or inner ear disorder. P1 is useful in treating slow digestion or slow
CC stomach emptying. P1 is useful in relieving symptoms of gastroparesis
CC such as nausea, vomiting, bloating, and delayed gastric emptying. P1 is
CC useful for treating or preventing asthma, nephritis, hepatitis,
CC pancreatitis, allergies, etc. P1 is useful for treating or preventing
CC type II diabetes mellitus, hyperglycaemia, respiratory disorders
CC including inhalation. P1 is useful in treating or preventing retinopathy,
CC nephropathy and edema formation. P1 is useful for treating or preventing
CC headache, anxiety, sleep disorders and memory loss. P1 is useful as a
CC marker to identify, detect, stage, or diagnosis diseases and conditions
CC of the small intestine, including Crohn's disease, colitis, inflammatory
CC bowel disease, tumours, etc. P1 can be conjugated to diagnostic or
CC therapeutic molecule to target cells bearing GC-C receptor, e.g., cystic
CC fibrosis lesions and specific cells lining the intestinal tract, thus
CC useful in targeting radioactive moieties or therapeutic moieties to the

CC intestine to aid in imaging and diagnosing or treating
CC colorectal/metastasised or local colorectal cancer. The current sequence
CC represents an oligonucleotide used in an example from the invention in
CC the prepartion of variant ST peptides and wild-type ST peptide.
XX
SQ Sequence 69 BP; 24 A; 16 C; 11 G; 18 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.196	Length:	69
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	13	Gaps:	0

US-10-107-814-20 (1-16) x ADR48400 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         50 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 15
```

RESULT 14
ADR48399
ID ADR48399 standard; DNA; 69 BP.
XX
AC ADR48399;
XX
DT 04-NOV-2004 (first entry)
XX
DE Oligonucleotide MO3621.
XX
KW Gastrointestinal; antiinflammatory; laxative; cardiant; antiulcer;
KW anorectic; cardiovascular; cytostatic; analgesic; CNS; respiratory;
KW neuroprotective; vasotropic; auditory; antiemetic; antiasthmatic;
KW nephrotropic; hepatotropic; virucide; immunosuppressive; antiallergic;
KW antidiabetic; ophthalmological; tranquiliser; hypnotic; nootropic;
KW guanylate cyclase C; GC-C; receptor; gastrointestinal disorder;
KW irritable bowel syndrome; constipation; gastroesophageal reflux disease;
KW heartburn; dyspepsia; gastroparesis; Crohn's disease; ulcerative colitis;
KW inflammatory bowel disease; obesity; heart failure; cystic fibrosis;
KW cancer; respiratory disorder; neurological disorder; carbonate imbalance;
KW erectile dysfunction; inner ear disorder; slow digestion; nausea;
KW vomiting; bloating; asthma; nephritis; hepatitis; pancreatitis; allergy;
KW retinopathy; nephropathy; headache; anxiety; sleep disorder; ds.
XX
OS Unidentified.
XX
PN WO2004069165-A2.
XX
PD 19-AUG-2004.
XX
PF 28-JAN-2004; 2004WO-US002390.
XX
PR 28-JAN-2003; 2003US-0443098P.
PR 15-MAY-2003; 2003US-0471288P.
PR 12-NOV-2003; 2003US-0519460P.
XX
PA (MICR-) MICROBIA INC.
XX
PI Currie MG, Mahajan-Miklos S;
XX
DR WPI; 2004-604332/58.
XX
PT Novel purified peptide capable of activating the guanylate cyclase C
PT receptor, useful for treating obesity, congestive heart failure and
PT benign prostatic hyperplasia.
XX
PS Example 1; Page 39; 93pp; English.
XX
CC The invention relates to a purified peptide (P1) capable of activating
CC the guanylate cyclase C (GC-C) receptor. Further disclosed is a
CC pharmaceutical composition comprising the peptide of the invention. The
CC composition of the invention is useful for treating a gastrointestinal
CC disorder in a patient, which involves administering P1, where the
CC gastrointestinal disorder is gastrointestinal motility disorder,
CC irritable bowel syndrome, chronic constipation, a functional
CC gastrointestinal disorder, gastroesophageal reflux disease, functional
CC heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia,
CC gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-
CC obstruction, Crohn's disease, ulcerative colitis or inflammatory bowel
CC disease. The peptide of the invention is also useful for treating
CC obesity, congestive heart failure, cystic fibrosis or a patient suffering
CC from constipation. The P1/GC-C receptor agonist is useful for treating
CC cancer, respiratory disorder, neurological disorder, disorder associated
CC with carbonate imbalance, erectile dysfunction, insulin-related disorder
CC or inner ear disorder. P1 is useful in treating slow digestion or slow
CC stomach emptying. P1 is useful in relieving symptoms of gastroparesis
CC such as nausea, vomiting, bloating, and delayed gastric emptying. P1 is
CC useful for treating or preventing asthma, nephritis, hepatitis,
CC pancreatitis, allergies, etc. P1 is useful for treating or preventing
CC type II diabetes mellitus, hyperglycaemia, respiratory disorders
CC including inhalation. P1 is useful in treating or preventing retinopathy,
CC nephropathy and edema formation. P1 is useful for treating or preventing
CC headache, anxiety, sleep disorders and memory loss. P1 is useful as a
CC marker to identify, detect, stage, or diagnosis diseases and conditions
CC of the small intestine, including Crohn's disease, colitis, inflammatory
CC bowel disease, tumours, etc. P1 can be conjugated to diagnostic or
CC therapeutic molecule to target cells bearing GC-C receptor, e.g., cystic
CC fibrosis lesions and specific cells lining the intestinal tract, thus
CC useful in targeting radioactive moieties or therapeutic moieties to the
CC intestine to aid in imaging and diagnosing or treating
CC colorectal/metastasised or local colorectal cancer. The current sequence
CC represents an oligonucleotide used in an example from the invention in
CC the prepartion of variant ST peptides and wild-type ST peptide.
XX
SQ Sequence 69 BP; 18 A; 11 C; 16 G; 24 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.196	Length:	69
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	13	Gaps:	0

US-10-107-814-20 (1-16) x ADR48399 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         24 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 59
```

RESULT 15
ABA01860
ID ABA01860 standard; DNA; 72 BP.
XX
AC ABA01860;
XX
DT 01-FEB-2002 (first entry)
XX
DE Human thermostable enterotoxin STh coding fragment Sth72N5.
XX
KW Human; thermostable enterotoxin; STh; metastatic colorectal cancer;
KW guanyl cyclase-C; GC-C; STa; ds.
XX
OS Homo sapiens.
XX
PN FR2805994-A1.
XX
PD 14-SEP-2001.
XX
PF 10-MAR-2000; 2000FR-00003141.
XX
PR 10-MAR-2000; 2000FR-00003141.
XX
PA (INRG) INRA INST NAT RECH AGRONOMIQUE.
XX

PI Der Vartanian M, Batisson I;
XX
DR WPI; 2001-640835/74.
XX
PT New compound for detecting and treating metastatic colorectal cancer
PT comprises a conjugate of an STa peptide and an immunogenic protein which
PT binds to the guanyl cyclase-c receptor.
XX
PS Disclosure; Page 22; 126pp; French.
XX
CC The present invention relates to a conjugate which comprises an E. coli
CC thermostable enterotoxin (STa) peptide and an active molecule where the
CC STa peptide has a conformation such that it is capable of binding to the
CC guanyl cyclase-C (GC-C) receptor. This can be used in the specific
CC diagnosis and treatment of metastatic colorectal cancer. The present
CC sequence is a fragment of the human thermostable enterotoxin (STh) coding
CC sequence
XX
SQ Sequence 72 BP; 14 A; 18 C; 17 G; 23 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0.206	Length:	72
Score:	63.00	Matches:	10
Percent Similarity:	83.33%	Conservative:	0
Best Local Similarity:	83.33%	Mismatches:	2
Query Match:	66.32%	Indels:	0
DB:	4	Gaps:	0

US-10-107-814-20 (1-16) x ABA01860 (1-72)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         18 TGTGAACTTTGTTGTAATCCTGCCTGTACAGGATGT 53
```

Search completed: August 28, 2005, 12:50:01
Job time : 362 secs

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OM protein - nucleic search, using frame_plus_p2n model

Run on: August 28, 2005, 10:16:26 ; Search time 2135 Seconds
(without alignments)
285.259 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
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Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 34239544 seqs, 19032134700 residues

Total number of hits satisfying chosen parameters: 68479088

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Command line parameters:
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-Q=/cgn2_1/USPTO_spool/US10107814/runat_26082005_122651_15718/app_query.fasta_1.199
-DB=EST -QFMT=fastap -SUFFIX=p2n.rst -MINMATCH=0.1 -LOOPCL=0 -LOOPEXT=0
-UNITS=bits -START=1 -END=-1 -MATRIX=blosum62 -TRANS=human40.cdi -LIST=45
-DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100 -THR_MIN=0 -ALIGN=15 -MODE=LOCAL
-OUTFMT=pto -NORM=ext -HEAPSIZE=500 -MINLEN=0 -MAXLEN=2000000000
-USER=US10107814_@CGN_1_1_4352_@runat_26082005_122651_15718 -NCPU=6 -ICPU=3
-NO_MMAP -LARGEQUERY -NEG_SCORES=0 -WAIT -DSPBLOCK=100 -LONGLOG
-DEV_TIMEOUT=120 -WARN_TIMEOUT=30 -THREADS=1 -XGAPOP=10 -XGAPEXT=0.5 -FGAPOP=6
-FGAPEXT=7 -YGAPOP=10 -YGAPEXT=0.5 -DELOP=6 -DELEXT=7

Database : EST:*
1: gb_est1:*
2: gb_est2:*
3: gb_htc:*
4: gb_est3:*
5: gb_est4:*
6: gb_est5:*
7: gb_est6:*
8: gb_gss1:*
9: gb_gss2:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

	Result No.	Score	% Query Match	Length	DB	ID	Description
	1	92	96.8	194	9	AY410926	AY410926 Pan trogl
c	2	92	96.8	302	1	AI721056	AI721056 as69e05.x
	3	92	96.8	339	9	AY410925	AY410925 Homo sapi
	4	92	96.8	367	5	BX092859	BX092859 BX092859
c	5	92	96.8	455	2	AW009510	AW009510 ws83f10.x
c	6	92	96.8	496	5	BQ027704	BQ027704 UI-H-CO0-
	7	92	96.8	703	7	CO581337	CO581337 ILLUMIGEN
	8	92	96.8	716	7	CO580213	CO580213 ILLUMIGEN
	9	90	94.7	316	1	AA689133	AA689133 vq52b01.r
	10	88	92.6	427	4	BM446293	BM446293 1IL6A7.ab
c	11	84	88.4	252	7	CR460021	CR460021 CR460021
	12	84	88.4	268	1	AV061512	AV061512 AV061512
	13	84	88.4	281	1	AV062212	AV062212 AV062212
	14	84	88.4	286	1	AV061769	AV061769 AV061769
c	15	84	88.4	291	5	BX640323	BX640323 BX640323
	16	84	88.4	292	1	AA623232	AA623232 vi14f01.r
	17	84	88.4	298	1	AV068378	AV068378 AV068378
	18	84	88.4	325	1	AA518536	AA518536 vi17b09.r
	19	84	88.4	337	1	AA871087	AA871087 vq44h09.r
	20	84	88.4	339	7	H00004	H00004 1783-1 Zinc
	21	84	88.4	339	9	AY410927	AY410927 Mus muscu
	22	84	88.4	347	1	AA616951	AA616951 vi20e09.r
	23	84	88.4	382	6	CB809177	CB809177 AMGNNUC:C
	24	84	88.4	385	5	BY079705	BY079705 BY079705
	25	84	88.4	400	1	AA107073	AA107073 ml91b11.r
	26	84	88.4	410	1	AV066530	AV066530 AV066530
	27	84	88.4	410	7	W34409	W34409 ma98a05.r1
	28	84	88.4	414	1	AA084972	AA084972 zn13g11.r
	29	84	88.4	416	7	W30607	W30607 mc10b12.r1
	30	84	88.4	425	1	AA690362	AA690362 vt31b11.r
	31	84	88.4	437	1	AA097740	AA097740 mk17a10.r
	32	84	88.4	451	1	AA734245	AA734245 vt26c08.r
c	33	84	88.4	451	1	AA107035	AA107035 ml94h08.r
	34	84	88.4	461	1	AA606495	AA606495 vo52g02.r
	35	84	88.4	465	1	AA123180	AA123180 mq09b07.r
	36	84	88.4	465	1	AA463144	AA463144 vg85e05.r
	37	84	88.4	523	1	AA139503	AA139503 mq36d09.r
	38	84	88.4	525	1	AA623166	AA623166 vi13e05.r
	39	84	88.4	533	1	AA518016	AA518016 vi18f01.r
	40	84	88.4	553	1	AA929498	AA929498 vt40a07.r
c	41	84	88.4	563	7	CN542531	CN542531 UI-R-EB0-
	42	84	88.4	568	6	BY702902	BY702902 BY702902
	43	84	88.4	570	3	AK002364	AK002364 Mus muscu
	44	84	88.4	605	4	BG969327	BG969327 602836804
	45	84	88.4	608	7	CF423670	CF423670 lac97h04.

ALIGNMENTS

RESULT 1
AY410926
LOCUS AY410926 194 bp DNA linear GSS 16-DEC-2003
DEFINITION Pan troglodytes GUCA2B gene, VIRTUAL TRANSCRIPT, partial sequence, genomic survey sequence.
ACCESSION AY410926
VERSION AY410926.1 GI:39766894
KEYWORDS GSS.
SOURCE Pan troglodytes (chimpanzee)
ORGANISM Pan troglodytes
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Pan.
REFERENCE 1 (bases 1 to 194)
AUTHORS Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A., Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B., Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J., Adams,M.D. and Cargill,M.
TITLE Inferring nonneutral evolution from human-chimp-mouse orthologous gene trios
JOURNAL Science 302 (5652), 1960-1963 (2003)
PUBMED 14671302
REFERENCE 2 (bases 1 to 194)
AUTHORS Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A., Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B., Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J., Adams,M.D. and Cargill,M.
TITLE Direct Submission
JOURNAL Submitted (16-NOV-2003) Celera Genomics, 45 West Gude Drive, Rockville, MD 20850, USA
COMMENT This sequence was made by sequencing genomic exons and ordering them based on alignment.
FEATURES Location/Qualifiers
source 1. .194

```
                  /organism="Pan troglodytes"
                  /mol_type="genomic DNA"
                  /db_xref="taxon:9598"
     gene         <1. .>194
                  /gene="GUCA2B"
                  /locus_tag="HCM4053"
ORIGIN

Alignment Scores:
Pred. No.:              0.000186      Length:         194
Score:                  92.00         Matches:        15
Percent Similarity:     100.00%       Conservative:   1
Best Local Similarity:  93.75%        Mismatches:     0
Query Match:            96.84%        Indels:         0
DB:                     9             Gaps:           0

US-10-107-814-20 (1-16) x AY410926 (1-194)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        144 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 191

RESULT 2
AI721056/c
LOCUS       AI721056                302 bp    mRNA    linear   EST 10-JUN-1999
DEFINITION  as69e05.x1 Barstead colon HPLRB7 Homo sapiens cDNA clone
            IMAGE:2333984 3' similar to SW:GUAU_HUMAN Q16661 UROGUANYLIN
            PRECURSOR ;, mRNA sequence.
ACCESSION   AI721056
VERSION     AI721056.1  GI:5038312
KEYWORDS    EST.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 302)
  AUTHORS   Hillier,L., Allen,M., Bowles,L., Dubuque,T., Geisel,G., Jost,S.,
            Krizman,D., Kucaba,T., Lacy,M., Le,N., Lennon,G., Marra,M.,
            Martin,J., Moore,B., Schellenberg,K., Steptoe,M., Tan,F.,
            Theising,B., White,Y., Wylie,T., Waterston,R. and Wilson,R.
  TITLE     WashU-NCI human EST Project
  JOURNAL   Unpublished (1997)
COMMENT     Contact: Wilson RK
            Washington University School of Medicine
            4444 Forest Park Parkway, Box 8501, St. Louis, MO 63108
            Tel: 314 286 1800
            Fax: 314 286 1810
            Email: est@watson.wustl.edu
            This clone is available royalty-free through LLNL ; contact the
            IMAGE Consortium (info@image.llnl.gov) for further information.
            Seq primer: -40UP from Gibco.
FEATURES              Location/Qualifiers
     source           1. .302
                      /organism="Homo sapiens"
                      /mol_type="mRNA"
                      /db_xref="taxon:9606"
                      /clone="IMAGE:2333984"
                      /sex="male"
                      /dev_stage="adult, age 25"
                      /lab_host="DH10B (phage resistant)"
                      /clone_lib="Barstead colon HPLRB7"
                      /note="Organ: colon; Vector: pT7T3D-Pac (Pharmacia) with a
                      modified polylinker; Site_1: EcoRI; Site_2: NotI; 1st
                      strand cDNA was primed with a Not I - oligo(dT) primer [5'
                      TGTTACGAATCTGAAGTGGGAGCGGCCGCCCTTTTTTTTTTTTTTTTTTTTTTT
                      3']; double-stranded cDNA was ligated to Eco RI adaptors
                      [5' AATTCACTAGTAAT 3' and 5' ATTACTAGTG 3'], digested
                      with Not I and cloned into the Not I and Eco RI sites of
                      the modified pT7T3 vector. Library constructed by Bob
                      Barstead."
ORIGIN

Alignment Scores:
Pred. No.:              0.000304      Length:         302
Score:                  92.00         Matches:        15
Percent Similarity:     100.00%       Conservative:   1
Best Local Similarity:  93.75%        Mismatches:     0
Query Match:            96.84%        Indels:         0
DB:                     1             Gaps:           0

US-10-107-814-20 (1-16) x AI721056 (1-302)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        268 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 221

RESULT 3
AY410925
LOCUS       AY410925                339 bp    DNA     linear   GSS 16-DEC-2003
DEFINITION  Homo sapiens GUCA2B gene, VIRTUAL TRANSCRIPT, partial sequence,
            genomic survey sequence.
ACCESSION   AY410925
VERSION     AY410925.1  GI:39766893
KEYWORDS    GSS.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 339)
  AUTHORS   Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A.,
            Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B.,
            Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J.,
            Adams,M.D. and Cargill,M.
  TITLE     Inferring nonneutral evolution from human-chimp-mouse orthologous
            gene trios
  JOURNAL   Science 302 (5652), 1960-1963 (2003)
   PUBMED   14671302
REFERENCE   2  (bases 1 to 339)
  AUTHORS   Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A.,
            Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B.,
            Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J.,
            Adams,M.D. and Cargill,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (16-NOV-2003) Celera Genomics, 45 West Gude Drive,
            Rockville, MD 20850, USA
COMMENT     This sequence was made by sequencing genomic exons and ordering
            them based on alignment.
FEATURES              Location/Qualifiers
     source           1. .339
                      /organism="Homo sapiens"
                      /mol_type="genomic DNA"
                      /db_xref="taxon:9606"
     gene             <1. .>339
                      /gene="GUCA2B"
                      /locus_tag="HCM4053"
ORIGIN

Alignment Scores:
Pred. No.:              0.000345      Length:         339
Score:                  92.00         Matches:        15
Percent Similarity:     100.00%       Conservative:   1
Best Local Similarity:  93.75%        Mismatches:     0
Query Match:            96.84%        Indels:         0
DB:                     9             Gaps:           0

US-10-107-814-20 (1-16) x AY410925 (1-339)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        289 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 336

RESULT 4
BX092859
LOCUS       BX092859                367 bp    mRNA    linear   EST 23-JAN-2003
DEFINITION  BX092859 Barstead colon HPLRB7 Homo sapiens cDNA clone
            IMAGp998G095790 ; IMAGE:2333984, mRNA sequence.
```

ACCESSION BX092859
VERSION BX092859.1 GI:27826487
KEYWORDS EST.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 367)
AUTHORS Ebert,L., Heil,O., Hennig,S., Neubert,P., Partsch,E., Peters,M., Radelof,U., Schneider,D. and Korn,B.
TITLE Human UnigeneSet - RZPD3
JOURNAL Unpublished (2003)
COMMENT Contact: Ina Rolfs
RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH
Im Neuenheimer Feld 580, D-69120 Heidelberg, Germany
RZPD; IMAGp998G095790.
RZPDLIB; I.M.A.G.E. cDNA Clone Collection;
Human UnigeneSet - RZPD3 (RZPDLIB No.972)
http://www.rzpd.de/CloneCards/cgi-bin/showLib.pl.cgi/response?libNo=972 Contact: Ina Rolfs
RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH
Heubnerweg 6, D-14059 Berlin, Germany
Tel: +49 30 32639 101
Fax: +49 30 32639 111
www.rzpd.de
This clone is available royalty-free from RZPD;
contact RZPD (clone@rzpd.de) for further information. Seq primer: M13r, Primer sequence: TTTCACACAGGAAACAGCTATGAC.

FEATURES Location/Qualifiers
source 1. .367
/organism="Homo sapiens"
/mol_type="mRNA"
/db_xref="taxon:9606"
/clone="IMAGp998G095790 ; IMAGE:2333984"
/sex="male"
/dev_stage="adult, age 25"
/lab_host="DH10B (phage resistant)"
/clone_lib="Barstead colon HPLRB7"
/note="Organ: colon; Vector: pT7T3D-Pac (Pharmacia) with a modified polylinker; Site_1: EcoRI; Site_2: NotI; 1st strand cDNA was primed with a Not I - oligo(dT) primer [5' TGTTACGAATCTGAAGTGGGAGCGGCCGCCCTTTTTTTTTTTTTTTTTTTTTTTT 3']; double-stranded cDNA was ligated to Eco RI adaptors [5' AATTCACTAGTAAT 3' and 5' ATTACTAGTG 3'], digested with Not I and cloned into the Not I and Eco RI sites of the modified pT7T3 vector. Library constructed by Bob Barstead."

ORIGIN

Alignment Scores:

Pred. No.:	0.000377	Length:	367
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	5	Gaps:	0

US-10-107-814-20 (1-16) x BX092859 (1-367)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db         77 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 124
```

RESULT 5
AW009510/c
LOCUS AW009510 455 bp mRNA linear EST 08-MAR-2000
DEFINITION ws83f10.x1 NCI_CGAP_Co3 Homo sapiens cDNA clone IMAGE:2504587 3' similar to SW:GUAU_HUMAN Q16661 UROGUANYLIN PRECURSOR ;, mRNA sequence.
ACCESSION AW009510
VERSION AW009510.1 GI:5858288
KEYWORDS EST.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 455)
AUTHORS NCI-CGAP http://www.ncbi.nlm.nih.gov/ncicgap.
TITLE National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index
JOURNAL Unpublished (1997)
COMMENT Contact: Robert Strausberg, Ph.D.
Email: cgapbs-r@mail.nih.gov
Tissue Procurement: Elias Campo, M.D., Michael R. Emmert-Buck, M.D., Ph.D.
cDNA Library Preparation: M. Bento Soares, Ph.D.
cDNA Library Arraying: Greg Lennon, Ph.D.
DNA Sequencing by: Washington University Genome Sequencing Center
Clone distribution: NCI-CGAP clone distribution information can be found through the I.M.A.G.E. Consortium/LLNL at:
www-bio.llnl.gov/bbrp/image/image.html
Insert Length: 651 Std Error: 0.00
Seq primer: -40UP from Gibco.

FEATURES Location/Qualifiers
source 1. .455
/organism="Homo sapiens"
/mol_type="mRNA"
/db_xref="taxon:9606"
/clone="IMAGE:2504587"
/sex="pooled"
/tissue_type="colon"
/lab_host="DH10B"
/clone_lib="NCI_CGAP_Co3"
/note="Vector: pT7T3D-Pac (Pharmacia) with a modified polylinker; Site_1: Not I; Site_2: Eco RI; 1st strand cDNA was prepared from 12 pooled bulk tumor samples and primed with a Not I - oligo(dT) primer. Double-stranded cDNA was ligated to Eco RI adaptors (Pharmacia), digested with Not I and cloned into the Not I and Eco RI sites of the modified pT7T3 vector. Library went through one round of normalization. "

ORIGIN

Alignment Scores:

Pred. No.:	0.000478	Length:	455
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	2	Gaps:	0

US-10-107-814-20 (1-16) x AW009510 (1-455)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        274 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTN 227
```

RESULT 6
BQ027704/c
LOCUS BQ027704 496 bp mRNA linear EST 27-MAR-2002
DEFINITION UI-H-CO0-ara-d-09-0-UI.s1 NCI_CGAP_Sub9 Homo sapiens cDNA clone IMAGE:3105831 3', mRNA sequence.
ACCESSION BQ027704
VERSION BQ027704.1 GI:19762983
KEYWORDS EST.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 496)
AUTHORS NCI-CGAP http://www.ncbi.nlm.nih.gov/ncicgap.
TITLE National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index
JOURNAL Unpublished (1997)
COMMENT Contact: Robert Strausberg, Ph.D.
Email: cgapbs-r@mail.nih.gov

Tissue Procurement: Dr. Jose Mercuende
cDNA Library preparation: Dr. M. Bento Soares, University of Iowa
cDNA Library Arrayed by: Dr. M. Bento Soares, University of Iowa
DNA Sequencing by: Dr. M. Bento Soares, University of Iowa
Clone Distribution: Clone distribution information can be found through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
Seq primer: M13 FORWARD
POLYA=Yes.

FEATURES Location/Qualifiers
source 1. .496
/organism="Homo sapiens"
/mol_type="mRNA"
/db_xref="taxon:9606"
/clone="IMAGE:3105831"
/tissue_type="mixed"
/dev_stage="mixed"
/lab_host="DH10B (Life Technologies)"
/clone_lib="NCI_CGAP_Sub9"
/note="Vector: pT7T3-Pac (Pharmacia) with a modified polylinker; Site_1: EcoR I; Site_2: Not I; tissues: Cholonic mucosa with Crohns disease, Cholonic mucosa with ulcerative colitis, Fetal thymus, Cervix, Cervical adenosquamous carcinoma, Ligament cells, Prostate carcinoma, Bladder carcinoma, Brain oligodenroga ; NCI_CGAP_Sub9 is a subtracted cDNA library constructed according to Bonaldo, Lennon and Soares, Genome Research, 6:791-806, 1996. First strand cDNA synthesis was primed with an oligo-dT primer containing a Not I site. Double stranded cDNA was ligated to an EcoR I adaptor, digested with Not I, and cloned directionally into pT7T3-Pac vector. The oligonucleotide used to prime the synthesis of first-strand cDNA contains a library tag sequence that is located between the Not I site and the (dT)18 tail. The sequence tags for this library are CGTC, AACG, GGGCC, GGAAG, TAGC, TAAGC, ATGG, AGACA, ATCAC. For additional information, contact: Bento Soares, bento-soares@uiowa.edu TAG_TISSUE=Colonic mucosa with Ulcerative Colitus TAG_LIB=UI-H-CO0 TAG_SEQ=TAGC"

ORIGIN

Alignment Scores:

Pred. No.:	0.000526	Length:	496
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	5	Gaps:	0

US-10-107-814-20 (1-16) x BQ027704 (1-496)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        297 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 250
```

RESULT 7
CO581337
LOCUS CO581337 703 bp mRNA linear EST 20-JUL-2004
DEFINITION ILLUMIGEN_MCQ_47368 Katze_MMJJ Macaca mulatta cDNA clone IBIUW:20016 5' similar to Bases 116 to 603 highly similar to human GUCA2B (Hs.32966), mRNA sequence.
ACCESSION CO581337
VERSION CO581337.1 GI:50412655
KEYWORDS EST.
SOURCE Macaca mulatta (rhesus monkey)
ORGANISM Macaca mulatta
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae; Macaca.
REFERENCE 1 (bases 1 to 703)
AUTHORS Katze,M.G., Thomas,M., Korth,M., Iadonato,S.P. and Magness,C.L.
TITLE Large-scale Rhesus Macaque cDNA Sequencing
JOURNAL Unpublished (2003)
COMMENT Contact: C. Magness
Illumigen Biosciences Inc.
2203 Airport Way S, Suite 450, Seattle, WA 98134, USA
Tel: 2063780400
Fax: 2063780408
Email: cmagness@illumigen.com
Sequenced on 2004.06.25. 622 Q20 bases. Library Preparation: Prof. Michael Katze Lab at University of Washington DNA Sequencing: Illumigen Biosciences Inc. For further information, see http://www.macaque.org
PCR PRimers
FORWARD: CCCTCACTAAAGGGAACAAAA
BACKWARD: CACTATAGGGCGAATTGGGTA
Insert Length: 703 Std Error: 0.00
Plate: CL000433 row: D column: 07
Seq primer: CCCTCACTAAAGGGAACAAAA
POLYA=Yes.

FEATURES Location/Qualifiers
source 1. .703
/organism="Macaca mulatta"
/mol_type="mRNA"
/strain="Indian"
/db_xref="taxon:9544"
/clone="IBIUW:20016"
/sex="female"
/dev_stage="adult"
/lab_host="Electromax DH10B"
/clone_lib="Katze_MMJJ"
/note="Organ: jejunum; Vector: pDONR 222; Site_1: BsrG I; Site_2: BsrG I; Created from CloneMiner cDNA Library Construction kit (catalog #18249-029)"

ORIGIN

Alignment Scores:

Pred. No.:	0.000773	Length:	703
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	7	Gaps:	0

US-10-107-814-20 (1-16) x CO581337 (1-703)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        308 AACGATGATTGTGAGCTGTGTGTGAACGTTGCATGTACCGGTTGCCTC 355
```

RESULT 8
CO580213
LOCUS CO580213 716 bp mRNA linear EST 20-JUL-2004
DEFINITION ILLUMIGEN_MCQ_48995 Katze_MMDD Macaca mulatta cDNA clone IBIUW:18172 5' similar to Bases 125 to 616 highly similar to human GUCA2B (Hs.32966), mRNA sequence.
ACCESSION CO580213
VERSION CO580213.1 GI:50411307
KEYWORDS EST.
SOURCE Macaca mulatta (rhesus monkey)
ORGANISM Macaca mulatta
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae; Macaca.
REFERENCE 1 (bases 1 to 716)
AUTHORS Katze,M.G., Thomas,M., Korth,M., Iadonato,S.P. and Magness,C.L.
TITLE Large-scale Rhesus Macaque cDNA Sequencing
JOURNAL Unpublished (2003)
COMMENT Contact: C. Magness
Illumigen Biosciences Inc.
2203 Airport Way S, Suite 450, Seattle, WA 98134, USA
Tel: 2063780400
Fax: 2063780408
Email: cmagness@illumigen.com
Sequenced on 2004.07.03. 605 Q20 bases. Library Preparation: Prof. Michael Katze Lab at University of Washington DNA Sequencing:

Illumigen Biosciences Inc. For further information, see
http://www.macaque.org
PCR PRimers
FORWARD: CCCTCACTAAAGGGAACAAAA
BACKWARD: CACTATAGGGCGAATTGGGTA
Insert Length: 716 Std Error: 0.00
Plate: CL000405 row: C column: 08
Seq primer: CCCTCACTAAAGGGAACAAAA
POLYA=Yes.

FEATURES Location/Qualifiers
source 1. .716
/organism="Macaca mulatta"
/mol_type="mRNA"
/strain="Indian"
/db_xref="taxon:9544"
/clone="IBIUW:18172"
/sex="male"
/dev_stage="adult"
/lab_host="Electromax DH10B"
/clone_lib="Katze_MMDD"
/note="Organ: duodenum; Vector: pDONR 222; Site_1: BsrG I; Site_2: BsrG I; Created from CloneMiner cDNA Library Construction kit (catalog #18249-029)"

ORIGIN

Alignment Scores:

Pred. No.:	0.000789	Length:	716
Score:	92.00	Matches:	15
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.75%	Mismatches:	0
Query Match:	96.84%	Indels:	0
DB:	7	Gaps:	0

US-10-107-814-20 (1-16) x CO580213 (1-716)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        317 AACGATGATTGTGAGCTGTGTGTGAACGTTGCATGTACCGGTTGCCTC 364
```

RESULT 9
AA689133
LOCUS AA689133 316 bp mRNA linear EST 12-DEC-1997
DEFINITION vq52b01.r1 Barstead mouse proximal colon MPLRB6 Mus musculus cDNA clone IMAGE:1105897 5' similar to TR:O09051 O09051 UROGUANYLIN. ;, mRNA sequence.
ACCESSION AA689133
VERSION AA689133.1 GI:2677855
KEYWORDS EST.
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE 1 (bases 1 to 316)
AUTHORS Marra,M., Hillier,L., Allen,M., Bowles,M., Dietrich,N., Dubuque,T., Geisel,S., Kucaba,T., Lacy,M., Le,M., Martin,J., Morris,M., Schellenberg,K., Steptoe,M., Tan,F., Underwood,K., Moore,B., Theising,B., Wylie,T., Lennon,G., Soares,B., Wilson,R. and Waterston,R.
TITLE The WashU-HHMI Mouse EST Project
JOURNAL Unpublished (1996)
COMMENT Contact: Marra M/Mouse EST Project
WashU-HHMI Mouse EST Project
Washington University School of MedicineP
4444 Forest Park Parkway, Box 8501, St. Louis, MO 63108
Tel: 314 286 1800
Fax: 314 286 1810
Email: mouseest@watson.wustl.edu
This clone is available royalty-free through LLNL ; contact the IMAGE Consortium (info@image.llnl.gov) for further information.
MGI:604065
Possible reversed clone: similarity on wrong strand
Seq primer: -28m13 rev2 ET from Amersham
High quality sequence stop: 21.

FEATURES Location/Qualifiers
source 1. .316
/organism="Mus musculus"
/mol_type="mRNA"
/strain="FVB/N"
/db_xref="taxon:10090"
/clone="IMAGE:1105897"
/dev_stage="7 day juvenile"
/lab_host="DH10B"
/clone_lib="Barstead mouse proximal colon MPLRB6"
/note="Vector: pT7T3D-Pac (Pharmacia) with a modified polylinker; Site_1: EcoRI; Site_2: NotI; 1st strand cDNA was primed with a Not I - oligo(dT) primer [5' TGTTACGAATCTGAAGTGGGAGCGGCCGCCCTTTTTTTTTTTTTTTTTTTTTTT 3']; double-stranded cDNA was ligated to Eco RI adaptors [AATTCGGATCCTTG], digested with Not I and cloned into the Not I and Eco RI sites of the modified pT7T3 vector. Library constructed by Bob Barstead. "

ORIGIN

Alignment Scores:

Pred. No.:	0.000645	Length:	316
Score:	90.00	Matches:	14
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	93.33%	Mismatches:	0
Query Match:	94.74%	Indels:	0
DB:	1	Gaps:	0

US-10-107-814-20 (1-16) x AA689133 (1-316)

```
Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||||:::||||||||||||||||||||
Db        272 AACGACGAATGTGAACTGTGTATAAATGTTGCCTGTACAGGCTGC 316
```

RESULT 10
BM446293
LOCUS BM446293 427 bp mRNA linear EST 05-FEB-2002
DEFINITION 1IL6A7.ab1 Bos taurus Ileum #1 library Bos taurus cDNA, mRNA sequence.
ACCESSION BM446293
VERSION BM446293.1 GI:18530449
KEYWORDS EST.
SOURCE Bos taurus (cow)
ORGANISM Bos taurus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Cetartiodactyla; Ruminantia; Pecora; Bovidae; Bovinae; Bos.
REFERENCE 1 (bases 1 to 427)
AUTHORS Hansen,C., Fu,A., Meng,Y., Li,C., Okine,E., Sensen,C.W., Gordon,P.M.K. and Moore,S.S.
TITLE Gene Expression Profiling of the Bovine Gastrointestinal Tract
JOURNAL Unpublished (2002)
COMMENT Contact: Dr. Stephen Moore
Beef Genomics Laboratory
Dept of AFNS, University of Alberta
410 Agri/For, Dept of AFNS, U of A, Edmonton, AB, T6G 2P5, Canada
Tel: 780 492 0169
Fax: 780 492 4265
Email: stephen.moore@ualberta.ca
Insert Length: 427 Std Error: 0.00
POLYA=No.

FEATURES Location/Qualifiers
source 1. .427
/organism="Bos taurus"
/mol_type="mRNA"
/db_xref="taxon:9913"
/tissue_type="Smooth muscle"
/cell_type="Simple columnar epithelial"
/dev_stage="Young adult"
/lab_host="XL1-BlueMRF'strain"
/clone_lib="Bos taurus Ileum #1 library"
/note="Organ: Intestine/ileum; Vector: Uni-2ZAPXR; Site_1: EcoRI; Site_2: Xho I"

```
ORIGIN

Alignment Scores:
Pred. No.:              0.00182        Length:         427
Score:                  88.00          Matches:        14
Percent Similarity:     100.00%        Conservative:   1
Best Local Similarity:  93.33%         Mismatches:     0
Query Match:            92.63%         Indels:         0
DB:                     4              Gaps:           0

US-10-107-814-20 (1-16) x BM446293 (1-427)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||:::|||||||||||||||||||||||||||||||||||||
Db        323 AACGACGACTGTGAGCTGTGTGTGAATGTTGCCTGTACCGGCTGC 367

RESULT 11
CR460021/c
LOCUS       CR460021                252 bp    mRNA    linear   EST 01-JUL-2004
DEFINITION  CR460021 Rat pBluescript Lion Rattus norvegicus cDNA clone
            LIONp463B03218 3', mRNA sequence.
ACCESSION   CR460021
VERSION     CR460021.1  GI:49592370
KEYWORDS    EST.
SOURCE      Rattus norvegicus (Norway rat)
  ORGANISM  Rattus norvegicus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae;
            Rattus.
REFERENCE   1  (bases 1 to 252)
  AUTHORS   Henrich,J., Hermanns,J., Kranz,H., Loebbert,R., Schlueter,T.,
            Schuette,D., Weindel,M., Heil,O., Ebert,L., Neubert,P., Peters,M.,
            Radelof,U., Schneider,D. and Korn,B.
  TITLE     Rat ArrayTAG cDNA
  JOURNAL   Unpublished (2004)
COMMENT     Contact: Inge Arlart
            RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH
            Heubnerweg 6, D-14059 Berlin, Germany
            Email: www.rzpd.de
            RZPD; LIONp463B03218.
            RZPDLIB;
            Rat ArrayTAG cDNA
            http://www.rzpd.de/cgi-
            bin/products/showLib.pl.cgi/response?libNo=463 Contact: Inge Arlart
            RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH
            Heubnerweg 6, D-14059 Berlin, Germany
            Tel: +49 30 32639 100
            Fax: +49 30 32639 111
            www.rzpd.de
            This clone is available royalty-free from RZPD;
            contact RZPD (clone@rzpd.de) for further information. Seq primer:
            RP: CAGGAAACAGCTATGAC.
FEATURES              Location/Qualifiers
     source           1. .252
                      /organism="Rattus norvegicus"
                      /mol_type="mRNA"
                      /db_xref="taxon:10116"
                      /clone="LIONp463B03218"
                      /lab_host="DH10B"
                      /clone_lib="Rat pBluescript Lion"
ORIGIN

Alignment Scores:
Pred. No.:              0.00414        Length:         252
Score:                  84.00          Matches:        13
Percent Similarity:     100.00%        Conservative:   1
Best Local Similarity:  92.86%         Mismatches:     0
Query Match:            88.42%         Indels:         0
DB:                     7              Gaps:           0

US-10-107-814-20 (1-16) x CR460021 (1-252)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||||:::||||||||||||||||||||||
Db        219 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 178

RESULT 12
AV061512
LOCUS       AV061512                268 bp    mRNA    linear   EST 23-JUN-1999
DEFINITION  AV061512 Mus musculus pancreas C57BL/6J adult Mus musculus cDNA
            clone 1810074F13, mRNA sequence.
ACCESSION   AV061512
VERSION     AV061512.1  GI:5161259
KEYWORDS    EST.
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 268)
  AUTHORS   Carninci,P., Shibata,K., Ozawa,Y., Konno,H., Itoh,M., Aizawa,K.,
            Akahira,S., Akiyama,J., Fukuda,S., Fukunishi,Y., Funayama,T.,
            Hara,A., Hayatsu,N., Hori,F., Ishikawa,T., Itoh,M., Izawa,M.,
            Kawai,J., Kikuchi,N., Kojima,Y., Matsuyama,T., Niitsuma,H., Oda,H.,
            Owa,C., Sato,K., Shibata,Y., Shigemoto,Y., Shiraki,T., Sogabe,Y.,
            Sugahara,Y., Suzuki,H., Suzuki,H., Tateno,M., Tomaru,Y.,
            Tominaga,N., Watanabe,S., Yagame,M., Yamamura,T., Yokota,T.,
            Yoshino,M., Muramatsu,M., Okazaki,Y. and Hayashizaki,Y.
  TITLE     RIKEN Mouse ESTs
  JOURNAL   Unpublished (1999)
COMMENT     Contact: Chie Owa
            Genome Science Laboratory
            RIKEN
            3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan
            Tel: 81-298-36-9145
            Fax: 81-298-36-9098
            Email: genome-res@rtc.riken.go.jp
            Thermostabilization and thermoactivation of thermolabile enzymes by
            trehalose and its application for the synthesis of full length cDNA
            (Proc. Natl. Acad. Sci. U.S.A. 95(2):520-524 (1998))
            Transcriptional sequencing: A method for DNA sequencing using RNA
            polymerase (Proc. Natl. Acad. Sci. U.S.A. 95(7):3455-3460 (1998))
            Please visit our web site (http://genome.rtc.riken.go.jp) for
            further details.
FEATURES              Location/Qualifiers
     source           1. .268
                      /organism="Mus musculus"
                      /mol_type="mRNA"
                      /strain="C57BL/6J"
                      /db_xref="taxon:10090"
                      /clone="1810074F13"
                      /sex="male"
                      /tissue_type="pancreas"
                      /dev_stage="adult"
                      /clone_lib="Mus musculus pancreas C57BL/6J adult"
ORIGIN

Alignment Scores:
Pred. No.:              0.00443        Length:         268
Score:                  84.00          Matches:        13
Percent Similarity:     100.00%        Conservative:   1
Best Local Similarity:  92.86%         Mismatches:     0
Query Match:            88.42%         Indels:         0
DB:                     1              Gaps:           0

US-10-107-814-20 (1-16) x AV061512 (1-268)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||||:::||||||||||||||||||||||
Db         39 GACGAATGTGAACTGTGTATAAATGTTGCCTGTACAGGCTGC 80

RESULT 13
AV062212
LOCUS       AV062212                281 bp    mRNA    linear   EST 24-JUN-1999
DEFINITION  AV062212 Mus musculus small intestine C57BL/6J adult Mus musculus
            cDNA clone 2010002J01, mRNA sequence.
ACCESSION   AV062212
```

VERSION AV062212.1 GI:5182040
KEYWORDS EST.
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE 1 (bases 1 to 281)
AUTHORS Carninci,P., Shibata,K., Ozawa,Y., Konno,H., Itoh,M., Aizawa,K., Akahira,S., Akiyama,J., Fukuda,S., Fukunishi,Y., Funayama,T., Hara,A., Hayatsu,N., Hori,F., Ishikawa,T., Itoh,M., Izawa,M., Kawai,J., Kikuchi,N., Kojima,Y., Matsuyama,T., Niitsuma,H., Oda,H., Owa,C., Sato,K., Shibata,Y., Shigemoto,Y., Shiraki,T., Sogabe,Y., Sugahara,Y., Suzuki,H., Suzuki,H., Tateno,M., Tomaru,Y., Tominaga,N., Watanabe,S., Yagame,M., Yamamura,T., Yokota,T., Yoshino,M., Muramatsu,M., Okazaki,Y. and Hayashizaki,Y.
TITLE RIKEN Mouse ESTs
JOURNAL Unpublished (1999)
COMMENT Contact: Chie Owa
Genome Science Laboratory
RIKEN
3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan
Tel: 81-298-36-9145
Fax: 81-298-36-9098
Email: genome-res@rtc.riken.go.jp
Thermostabilization and thermoactivation of thermolabile enzymes by trehalose and its application for the synthesis of full length cDNA (Proc. Natl. Acad. Sci. U.S.A. 95(2):520-524 (1998))
Transcriptional sequencing: A method for DNA sequencing using RNA polymerase (Proc. Natl. Acad. Sci. U.S.A. 95(7):3455-3460 (1998))
Please visit our web site (http://genome.rtc.riken.go.jp) for further details.

FEATURES Location/Qualifiers
source 1. .281
/organism="Mus musculus"
/mol_type="mRNA"
/strain="C57BL/6J"
/db_xref="taxon:10090"
/clone="2010002J01"
/sex="male"
/tissue_type="small intestine"
/dev_stage="adult"
/clone_lib="Mus musculus small intestine C57BL/6J adult"

ORIGIN

Alignment Scores:

Pred. No.:	0.00467	Length:	281
Score:	84.00	Matches:	13
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	92.86%	Mismatches:	0
Query Match:	88.42%	Indels:	0
DB:	1	Gaps:	0

US-10-107-814-20 (1-16) x AV062212 (1-281)

```
Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
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Db         52 GACGAATGTGAACTGTGTATAAATGTTGCCTGTACAGGCTGC 93
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RESULT 14
AV061769
LOCUS AV061769 286 bp mRNA linear EST 24-JUN-1999
DEFINITION AV061769 Mus musculus small intestine C57BL/6J adult Mus musculus cDNA clone 2010001A15, mRNA sequence.
ACCESSION AV061769
VERSION AV061769.1 GI:5181597
KEYWORDS EST.
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE 1 (bases 1 to 286)
AUTHORS Carninci,P., Shibata,K., Ozawa,Y., Konno,H., Itoh,M., Aizawa,K., Akahira,S., Akiyama,J., Fukuda,S., Fukunishi,Y., Funayama,T., Hara,A., Hayatsu,N., Hori,F., Ishikawa,T., Itoh,M., Izawa,M., Kawai,J., Kikuchi,N., Kojima,Y., Matsuyama,T., Niitsuma,H., Oda,H., Owa,C., Sato,K., Shibata,Y., Shigemoto,Y., Shiraki,T., Sogabe,Y., Sugahara,Y., Suzuki,H., Suzuki,H., Tateno,M., Tomaru,Y., Tominaga,N., Watanabe,S., Yagame,M., Yamamura,T., Yokota,T., Yoshino,M., Muramatsu,M., Okazaki,Y. and Hayashizaki,Y.
TITLE RIKEN Mouse ESTs
JOURNAL Unpublished (1999)
COMMENT Contact: Chie Owa
Genome Science Laboratory
RIKEN
3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan
Tel: 81-298-36-9145
Fax: 81-298-36-9098
Email: genome-res@rtc.riken.go.jp
Thermostabilization and thermoactivation of thermolabile enzymes by trehalose and its application for the synthesis of full length cDNA (Proc. Natl. Acad. Sci. U.S.A. 95(2):520-524 (1998))
Transcriptional sequencing: A method for DNA sequencing using RNA polymerase (Proc. Natl. Acad. Sci. U.S.A. 95(7):3455-3460 (1998))
Please visit our web site (http://genome.rtc.riken.go.jp) for further details.

FEATURES Location/Qualifiers
source 1. .286
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/mol_type="mRNA"
/strain="C57BL/6J"
/db_xref="taxon:10090"
/clone="2010001A15"
/sex="male"
/tissue_type="small intestine"
/dev_stage="adult"
/clone_lib="Mus musculus small intestine C57BL/6J adult"

ORIGIN

Alignment Scores:

Pred. No.:	0.00476	Length:	286
Score:	84.00	Matches:	13
Percent Similarity:	100.00%	Conservative:	1
Best Local Similarity:	92.86%	Mismatches:	0
Query Match:	88.42%	Indels:	0
DB:	1	Gaps:	0

US-10-107-814-20 (1-16) x AV061769 (1-286)

```
Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
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Db         57 GACGAATGTGAACTGTGTATAAATGTTGCCTGTACAGGCTGC 98
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RESULT 15
BX640323/c
LOCUS BX640323 291 bp mRNA linear EST 12-AUG-2003
DEFINITION BX640323 pBluescript Lion Mus musculus cDNA clone LIONp462H12394 3', mRNA sequence.
ACCESSION BX640323
VERSION BX640323.1 GI:33620198
KEYWORDS EST.
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE 1 (bases 1 to 291)
AUTHORS Henrich,J., Hermanns,J., Kranz,H., Loebbert,R., Schlueter,T., Schuette,D., Weindel,M., Heil,O., Ebert,L., Neubert,P., Peters,M., Radelof,U., Schneider,D. and Korn,B.
TITLE Mouse ArrayTAG cDNA (LION)
JOURNAL Unpublished (2003)
COMMENT Contact: Ina Rolfs
RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH
Im Neuenheimer Feld 580, D-69120 Heidelberg, Germany
RZPD; LIONp462H12394.
RZPDLIB;
Mouse ArrayTAG cDNA (LION)

```
           http://www.rzpd.de/cgi-bin/products/showLib.pl.cgi/response?libNo=4
           62 Contact: Ina Rolfs
           RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH
           Heubnerweg 6, D-14059 Berlin, Germany
           Tel: +49 30 32639 101
           Fax: +49 30 32639 111
           www.rzpd.de
           This clone is available royalty-free from RZPD;
           contact RZPD (clone@rzpd.de) for further information. Seq primer:
           RP: CAGGAAACAGCTATGAC.
FEATURES             Location/Qualifiers
     source          1. .291
                     /organism="Mus musculus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10090"
                     /clone="LIONp462H12394"
                     /lab_host="DH10B"
                     /clone_lib="pBluescript Lion"
ORIGIN

Alignment Scores:
Pred. No.:              0.00485        Length:          291
Score:                  84.00          Matches:         13
Percent Similarity:     100.00%        Conservative:    1
Best Local Similarity:  92.86%         Mismatches:      0
Query Match:            88.42%         Indels:          0
DB:                     5              Gaps:            0

US-10-107-814-20 (1-16) x BX640323 (1-291)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||||:::||||||||||||||||||||
Db        237 GACGAATGTGAACTGTGTATAAATGTTGCCTGTACAGGCTGC 196


Search completed: August 28, 2005, 14:09:14
Job time : 2139 secs
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GenCore version 5.1.6
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OM protein - nucleic search, using frame_plus_p2n model

Run on: August 28, 2005, 12:36:41 ; Search time 133 Seconds
(without alignments)
196.845 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Xgapop 10.0 , Xgapext 0.5
Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 1202784 seqs, 818138359 residues

Total number of hits satisfying chosen parameters: 2405568

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Command line parameters:
-MODEL=frame+_p2n.model -DEV=xlh
-Q=/cgn2_1/USPTO_spool/US10107814/runat_26082005_122651_15738/app_query.fasta_1.199
-DB=Issued_Patents_NA -QFMT=fastap -SUFFIX=p2n.rni -MINMATCH=0.1 -LOOPCL=0
-LOOPEXT=0 -UNITS=bits -START=1 -END=-1 -MATRIX=blosum62 -TRANS=human40.cdi
-LIST=45 -DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100 -THR_MIN=0 -ALIGN=15
-MODE=LOCAL -OUTFMT=pto -NORM=ext -HEAPSIZE=500 -MINLEN=0 -MAXLEN=2000000000
-USER=US10107814_@CGN_1_1_177_@runat_26082005_122651_15738 -NCPU=6 -ICPU=3
-NO_MMAP -LARGEQUERY -NEG_SCORES=0 -WAIT -DSPBLOCK=100 -LONGLOG
-DEV_TIMEOUT=120 -WARN_TIMEOUT=30 -THREADS=1 -XGAPOP=10 -XGAPEXT=0.5 -FGAPOP=6
-FGAPEXT=7 -YGAPOP=10 -YGAPEXT=0.5 -DELOP=6 -DELEXT=7

Database : Issued_Patents_NA:*
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2: /cgn2_6/ptodata/1/ina/5B_COMB.seq:*
3: /cgn2_6/ptodata/1/ina/6A_COMB.seq:*
4: /cgn2_6/ptodata/1/ina/6B_COMB.seq:*
5: /cgn2_6/ptodata/1/ina/PCTUS_COMB.seq:*
6: /cgn2_6/ptodata/1/ina/backfiles1.seq:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	58	61.1	57	1	US-08-141-892A-1	Sequence 1, Appli
2	58	61.1	57	1	US-08-141-892A-4	Sequence 4, Appli
3	58	61.1	57	2	US-08-583-447A-1	Sequence 1, Appli
4	58	61.1	57	2	US-08-583-447A-4	Sequence 4, Appli
5	58	61.1	57	2	US-08-467-920-1	Sequence 1, Appli
6	58	61.1	57	2	US-08-467-920-4	Sequence 4, Appli
7	58	61.1	57	3	US-08-635-930-1	Sequence 1, Appli
8	58	61.1	57	3	US-08-635-930-4	Sequence 4, Appli
9	58	61.1	57	3	US-09-193-997-1	Sequence 1, Appli
10	58	61.1	57	3	US-09-193-997-4	Sequence 4, Appli
11	58	61.1	57	3	US-09-138-237A-1	Sequence 1, Appli
12	58	61.1	57	3	US-09-138-237A-4	Sequence 4, Appli
13	56	58.9	45	2	US-07-903-029-3	Sequence 3, Appli
14	56	58.9	589	2	US-07-903-029-2	Sequence 2, Appli
c 15	53	55.8	1119	4	US-09-543-681A-3299	Sequence 3299, Ap
c 16	53	55.8	78720	4	US-09-949-016-12710	Sequence 12710, A
c 17	53	55.8	78720	4	US-09-949-016-17283	Sequence 17283, A
18	52	54.7	136917	4	US-09-949-016-16369	Sequence 16369, A
19	50	52.6	74527	4	US-09-949-016-12339	Sequence 12339, A
20	50	52.6	74528	4	US-09-949-016-13275	Sequence 13275, A
21	49	51.6	4894	4	US-09-976-594-155	Sequence 155, App
c 22	49	51.6	134890	4	US-09-949-016-15602	Sequence 15602, A
c 23	48	50.5	601	4	US-09-949-016-158933	Sequence 158933,
c 24	48	50.5	601	4	US-09-949-016-158934	Sequence 158934,
25	48	50.5	789	4	US-09-627-536-11	Sequence 11, Appl
26	48	50.5	2419	4	US-09-627-536-10	Sequence 10, Appl
27	48	50.5	62354	4	US-09-949-016-16188	Sequence 16188, A
28	47.5	50.0	3318	4	US-09-949-016-3755	Sequence 3755, Ap
29	47.5	50.0	37030	4	US-08-311-731A-25	Sequence 25, Appl
30	47.5	50.0	245286	4	US-09-949-016-15497	Sequence 15497, A
31	47	49.5	601	4	US-09-949-016-40527	Sequence 40527, A
32	47	49.5	601	4	US-09-949-016-63866	Sequence 63866, A
33	47	49.5	601	4	US-09-949-016-63941	Sequence 63941, A
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35	47	49.5	809	4	US-09-270-767-12276	Sequence 12276, A
c 36	47	49.5	69062	4	US-09-949-016-13608	Sequence 13608, A
c 37	47	49.5	69062	4	US-09-949-016-13609	Sequence 13609, A
c 38	47	49.5	69687	4	US-09-949-016-12890	Sequence 12890, A
39	47	49.5	90724	4	US-09-949-016-16601	Sequence 16601, A
40	47	49.5	325034	4	US-09-949-016-14957	Sequence 14957, A
41	47	49.5	389504	4	US-09-949-016-11774	Sequence 11774, A
42	47	49.5	4403765	3	US-09-103-840A-2	Sequence 2, Appli
43	47	49.5	4411529	3	US-09-103-840A-1	Sequence 1, Appli
44	46.5	48.9	87629	4	US-09-949-016-15262	Sequence 15262, A
45	46.5	48.9	87629	4	US-09-949-016-15263	Sequence 15263, A

ALIGNMENTS

RESULT 1
US-08-141-892A-1
; Sequence 1, Application US/08141892A
; Patent No. 5518888
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: ST Receptor Binding Compounds and Methods
; TITLE OF INVENTION: of Using the Same
; NUMBER OF SEQUENCES: 54
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
; STREET: One Liberty Place - 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: U.S.A.
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: 3.5 inch disk, 720 Kb
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: WordPerfect 5.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/141,892A
; FILING DATE: 26-OCT-1993
; CLASSIFICATION: 435
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER:
; FILING DATE:
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-0903
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 1:

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;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-141-892A-1

Alignment Scores:
Pred. No.:              0.152          Length:         57
Score:                  58.00          Matches:        9
Percent Similarity:     75.00%         Conservative:   0
Best Local Similarity:  75.00%         Mismatches:     3
Query Match:            61.05%         Indels:         0
DB:                     1              Gaps:           0

US-10-107-814-20 (1-16) x US-08-141-892A-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54

RESULT 2
US-08-141-892A-4
; Sequence 4, Application US/08141892A
; Patent No. 5518888
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and Methods
;    TITLE OF INVENTION:  of Using the Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
;      STREET:  One Liberty Place - 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  U.S.A.
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  3.5 inch disk, 720 Kb
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/141,892A
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-0903
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  4:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-141-892A-4

Alignment Scores:
Pred. No.:              0.152          Length:         57
Score:                  58.00          Matches:        9
Percent Similarity:     75.00%         Conservative:   0
Best Local Similarity:  75.00%         Mismatches:     3
Query Match:            61.05%         Indels:         0
DB:                     1              Gaps:           0

US-10-107-814-20 (1-16) x US-08-141-892A-4 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54

RESULT 3
US-08-583-447A-1
; Sequence 1, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-583-447A-1

Alignment Scores:
Pred. No.:              0.152          Length:         57
Score:                  58.00          Matches:        9
Percent Similarity:     75.00%         Conservative:   0
Best Local Similarity:  75.00%         Mismatches:     3
Query Match:            61.05%         Indels:         0
DB:                     2              Gaps:           0

US-10-107-814-20 (1-16) x US-08-583-447A-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
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Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54

RESULT 4
US-08-583-447A-4
; Sequence 4, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  4:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-583-447A-4

Alignment Scores:
Pred. No.:                0.152          Length:          57
Score:                    58.00          Matches:         9
Percent Similarity:       75.00%         Conservative:    0
Best Local Similarity:    75.00%         Mismatches:      3
Query Match:              61.05%         Indels:          0
DB:                       2              Gaps:            0

US-10-107-814-20 (1-16) x US-08-583-447A-4 (1-57)

Qy           4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
               ||||||||||||   |||   ||||||   ||||||
Db     -    19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54

RESULT 5
US-08-467-920-1
; Sequence 1, Application US/08467920
; Patent No. 5962220
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically
;    TITLE OF INVENTION:  Bind To Colorectal Cancer Cells
;    TITLE OF INVENTION:  And Methods Of Using The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz &
;      ADDRESSEE:  No. 5962220ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.0
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/467,920
;      FILING DATE:
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1589
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-467-920-1

Alignment Scores:
Pred. No.:                0.152          Length:          57
Score:                    58.00          Matches:         9
Percent Similarity:       75.00%         Conservative:    0
Best Local Similarity:    75.00%         Mismatches:      3
Query Match:              61.05%         Indels:          0
DB:                       2              Gaps:            0

US-10-107-814-20 (1-16) x US-08-467-920-1 (1-57)

Qy           4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
               ||||||||||||   |||   ||||||   ||||||
Db          19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54

RESULT 6
US-08-467-920-4
; Sequence 4, Application US/08467920
; Patent No. 5962220
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically
;    TITLE OF INVENTION:  Bind To Colorectal Cancer Cells
;    TITLE OF INVENTION:  And Methods Of Using The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz &
;      ADDRESSEE:  No. 5962220ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
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;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.0
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/467,920
;      FILING DATE:
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1589
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  4:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-467-920-4

Alignment Scores:
Pred. No.:                0.152          Length:         57
Score:                    58.00          Matches:        9
Percent Similarity:       75.00%         Conservative:   0
Best Local Similarity:    75.00%         Mismatches:     3
Query Match:              61.05%         Indels:         0
DB:                       2              Gaps:           0

US-10-107-814-20 (1-16) x US-08-467-920-4 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54

RESULT 7
US-08-635-930-1
; Sequence 1, Application US/08635930
; Patent No. 6060037
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically Bind To
;    TITLE OF INVENTION:  Colorectal Cancer Cells And Methods Of Using
;    TITLE OF INVENTION:  The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 6060037ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  WINDOWS 3.1
;      SOFTWARE:  WordPerfect 6.0/6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/635,930
;      FILING DATE:  26-APR-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/305,056
;      FILING DATE:  13-SEP-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1360
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-635-930-1

Alignment Scores:
Pred. No.:                0.152          Length:         57
Score:                    58.00          Matches:        9
Percent Similarity:       75.00%         Conservative:   0
Best Local Similarity:    75.00%         Mismatches:     3
Query Match:              61.05%         Indels:         0
DB:                       3              Gaps:           0

US-10-107-814-20 (1-16) x US-08-635-930-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54

RESULT 8
US-08-635-930-4
; Sequence 4, Application US/08635930
; Patent No. 6060037
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically Bind To
;    TITLE OF INVENTION:  Colorectal Cancer Cells And Methods Of Using
;    TITLE OF INVENTION:  The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 6060037ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  WINDOWS 3.1
;      SOFTWARE:  WordPerfect 6.0/6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/635,930
;      FILING DATE:  26-APR-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/305,056
;      FILING DATE:  13-SEP-1994
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; CLASSIFICATION: 435
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-1360
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 4:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 57 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: both
; MOLECULE TYPE: cDNA
; FEATURE:
; NAME/KEY: CDS
; LOCATION: 1..57
US-08-635-930-4

Alignment Scores:

Pred. No.:	0.152	Length:	57
Score:	58.00	Matches:	9
Percent Similarity:	75.00%	Conservative:	0
Best Local Similarity:	75.00%	Mismatches:	3
Query Match:	61.05%	Indels:	0
DB:	3	Gaps:	0

US-10-107-814-20 (1-16) x US-08-635-930-4 (1-57)

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Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              |||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54
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RESULT 9
US-09-193-997-1
; Sequence 1, Application US/09193997
; Patent No. 6087109
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: Compositions That Specifically
; TITLE OF INVENTION: Bind To Colorectal Cancer Cells
; TITLE OF INVENTION: And Methods Of Using The Same
; NUMBER OF SEQUENCES: 54
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz &
; ADDRESSEE: No. 6087109ris
; STREET: One Liberty Place, 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: USA
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: WordPerfect 5.0
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/09/193,997
; FILING DATE:
; CLASSIFICATION:
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: 08/467,920
; FILING DATE:
; CLASSIFICATION:
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-1589
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 57 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: both
; MOLECULE TYPE: cDNA
; FEATURE:
; NAME/KEY: CDS
; LOCATION: 1..57
US-09-193-997-1

Alignment Scores:

Pred. No.:	0.152	Length:	57
Score:	58.00	Matches:	9
Percent Similarity:	75.00%	Conservative:	0
Best Local Similarity:	75.00%	Mismatches:	3
Query Match:	61.05%	Indels:	0
DB:	3	Gaps:	0

US-10-107-814-20 (1-16) x US-09-193-997-1 (1-57)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              |||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54
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RESULT 10
US-09-193-997-4
; Sequence 4, Application US/09193997
; Patent No. 6087109
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: Compositions That Specifically
; TITLE OF INVENTION: Bind To Colorectal Cancer Cells
; TITLE OF INVENTION: And Methods Of Using The Same
; NUMBER OF SEQUENCES: 54
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz &
; ADDRESSEE: No. 6087109ris
; STREET: One Liberty Place, 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: USA
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: WordPerfect 5.0
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/09/193,997
; FILING DATE:
; CLASSIFICATION:
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: 08/467,920
; FILING DATE:
; CLASSIFICATION:
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-1589
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 4:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 57 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: both
; MOLECULE TYPE: cDNA
; FEATURE:
; NAME/KEY: CDS
; LOCATION: 1..57

US-09-193-997-4

Alignment Scores:

Pred. No.:	0.152	Length:	57
Score:	58.00	Matches:	9
Percent Similarity:	75.00%	Conservative:	0
Best Local Similarity:	75.00%	Mismatches:	3
Query Match:	61.05%	Indels:	0
DB:	3	Gaps:	0

US-10-107-814-20 (1-16) x US-09-193-997-4 (1-57)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54
```

RESULT 11
US-09-138-237A-1
; Sequence 1, Application US/09138237A
; Patent No. 6268159
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: ST Receptor Binding Compounds and Methods
; TITLE OF INVENTION: of Using the Same
; NUMBER OF SEQUENCES: 54
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz and No. 6268159ris
; STREET: One Liberty Place - 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: U.S.A.
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: 3.5 inch disk, 720 Kb
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: WordPerfect 5.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/09/138,237A
; FILING DATE:
; CLASSIFICATION:
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: 08/141,892
; FILING DATE:
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-0903
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 1:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 57 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: both
; MOLECULE TYPE: cDNA
; FEATURE:
; NAME/KEY: CDS
; LOCATION: 1..57
US-09-138-237A-1

Alignment Scores:

Pred. No.:	0.152	Length:	57
Score:	58.00	Matches:	9
Percent Similarity:	75.00%	Conservative:	0
Best Local Similarity:	75.00%	Mismatches:	3
Query Match:	61.05%	Indels:	0
DB:	3	Gaps:	0

US-10-107-814-20 (1-16) x US-09-138-237A-1 (1-57)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54
```

RESULT 12
US-09-138-237A-4
; Sequence 4, Application US/09138237A
; Patent No. 6268159
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: ST Receptor Binding Compounds and Methods
; TITLE OF INVENTION: of Using the Same
; NUMBER OF SEQUENCES: 54
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz and No. 6268159ris
; STREET: One Liberty Place - 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: U.S.A.
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: 3.5 inch disk, 720 Kb
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: WordPerfect 5.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/09/138,237A
; FILING DATE:
; CLASSIFICATION:
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: 08/141,892
; FILING DATE:
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-0903
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 4:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 57 base pairs
; TYPE: nucleic acid
; STRANDEDNESS: double
; TOPOLOGY: both
; MOLECULE TYPE: cDNA
; FEATURE:
; NAME/KEY: CDS
; LOCATION: 1..57
US-09-138-237A-4

Alignment Scores:

Pred. No.:	0.152	Length:	57
Score:	58.00	Matches:	9
Percent Similarity:	75.00%	Conservative:	0
Best Local Similarity:	75.00%	Mismatches:	3
Query Match:	61.05%	Indels:	0
DB:	3	Gaps:	0

US-10-107-814-20 (1-16) x US-09-138-237A-4 (1-57)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54
```

RESULT 13
US-07-903-029-3
; Sequence 3, Application US/07903029
; Patent No. 5969097
; GENERAL INFORMATION:
; APPLICANT: Wiegand, Roger C.
; APPLICANT: Currie, Mark C.
; APPLICANT: Fok, Kam F.

```
;    TITLE OF INVENTION:  Human Guanylin
;    NUMBER OF SEQUENCES:  6
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Dennis A. Bennett, Monsanto Co., A3SG
;      STREET:  800 N. Lindbergh Blvd.
;      CITY:  St. Louis
;      STATE:  Missouri
;      COUNTRY:  USA
;      ZIP:  63167
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/07/903,029
;      FILING DATE:  19920623
;      CLASSIFICATION:  530
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Bennett, Dennis A.
;      REGISTRATION NUMBER:  34,547
;      REFERENCE/DOCKET NUMBER:  07-21(872)A
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (314)694-5402
;      TELEFAX:  (314)694-9009
;  INFORMATION FOR SEQ ID NO:  3:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  45 base pairs
;      TYPE:  NUCLEIC ACID
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  cDNA
US-07-903-029-3

Alignment Scores:
Pred. No.:                0.235          Length:          45
Score:                    56.00          Matches:          8
Percent Similarity:       75.00%         Conservative:     1
Best Local Similarity:    66.67%         Mismatches:       3
Query Match:              58.95%         Indels:           0
DB:                       2              Gaps:             0

US-10-107-814-20 (1-16) x US-07-903-029-3 (1-45)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||:::|||          ||||||||||||||
Db         10 TGTGAAATCTGTGCCTACGCTGCCTGTACCGGATGC 45

RESULT 14
US-07-903-029-2
; Sequence 2, Application US/07903029
; Patent No. 5969097
;  GENERAL INFORMATION:
;    APPLICANT:  Wiegand, Roger C.
;    APPLICANT:  Currie, Mark C.
;    APPLICANT:  Fok, Kam F.
;    TITLE OF INVENTION:  Human Guanylin
;    NUMBER OF SEQUENCES:  6
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Dennis A. Bennett, Monsanto Co., A3SG
;      STREET:  800 N. Lindbergh Blvd.
;      CITY:  St. Louis
;      STATE:  Missouri
;      COUNTRY:  USA
;      ZIP:  63167
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/07/903,029
;      FILING DATE:  19920623
;      CLASSIFICATION:  530
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Bennett, Dennis A.
;      REGISTRATION NUMBER:  34,547
;      REFERENCE/DOCKET NUMBER:  07-21(872)A
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (314)694-5402
;      TELEFAX:  (314)694-9009
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  589 base pairs
;      TYPE:  NUCLEIC ACID
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  cDNA
US-07-903-029-2

Alignment Scores:
Pred. No.:                4.7            Length:          589
Score:                    56.00          Matches:          8
Percent Similarity:       75.00%         Conservative:     1
Best Local Similarity:    66.67%         Mismatches:       3
Query Match:              58.95%         Indels:           0
DB:                       2              Gaps:             0

US-10-107-814-20 (1-16) x US-07-903-029-2 (1-589)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||:::|||          ||||||||||||||
Db        318 TGTGAAATCTGTGCCTACGCTGCCTGTACCGGATGC 353

RESULT 15
US-09-543-681A-3299/c
; Sequence 3299, Application US/09543681A
; Patent No. 6605709
; GENERAL INFORMATION:
;  APPLICANT: GARY BRETON
;  TITLE OF INVENTION: NUCLEIC ACID AND AMINO ACID SEQUENCES RELATING TO PROTEUS MIRABII
;  TITLE OF INVENTION:  DIAGNOSTICS AND THERAPEUTICS
;  FILE REFERENCE: 2709.1002-001
;  CURRENT APPLICATION NUMBER: US/09/543,681A
;  CURRENT FILING DATE:  2000-04-05
;  PRIOR APPLICATION NUMBER: US 60/128,706
;  PRIOR FILING DATE: 1999-04-09
;  NUMBER OF SEQ ID NOS: 8344
; SEQ ID NO 3299
;   LENGTH: 1119
;   TYPE: DNA
;   ORGANISM: Proteus mirabilis
US-09-543-681A-3299

Alignment Scores:
Pred. No.:                29             Length:          1119
Score:                    53.00          Matches:          5
Percent Similarity:       78.57%         Conservative:     6
Best Local Similarity:    35.71%         Mismatches:       3
Query Match:              55.79%         Indels:           0
DB:                       4              Gaps:             0

US-10-107-814-20 (1-16) x US-09-543-681A-3299 (1-1119)

Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ::::::|||::::::|||:::   :::   ||||||   |||
Db        255 AACCAGTGTGATATGTGCATCAGGATAATGTGCACGAATTGC 214


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Job time : 138 secs
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GenCore version 5.1.6
Copyright (c) 1993 - 2005 Compugen Ltd.

OM protein - nucleic search, using frame_plus_p2n model

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232.127 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
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-TRANS=human40.cdi -LIST=45 -DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100
-THR_MIN=0 -ALIGN=15 -MODE=LOCAL -OUTFMT=pto -NORM=ext -HEAPSIZE=500 -MINLEN=0
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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

	Result No.	Score	% Query Match	Length	DB	ID	Description
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	2	92	96.8	3404	22	US-10-737-082-6	Sequence 6, Appli
	3	92	96.8	3404	22	US-10-765-790-6	Sequence 6, Appli
	4	84	88.4	651	9	US-09-917-800A-1700	Sequence 1700, Ap
	5	63	66.3	69	20	US-10-766-735-62	Sequence 62, Appl
c	6	63	66.3	69	20	US-10-766-735-63	Sequence 63, Appl
	7	63	66.3	69	21	US-10-796-719-62	Sequence 62, Appl
c	8	63	66.3	69	21	US-10-796-719-63	Sequence 63, Appl
	9	63	66.3	214	20	US-10-425-821-88	Sequence 88, Appl
	10	63	66.3	950	21	US-10-489-273-1	Sequence 1, Appli
	11	63	66.3	1183	21	US-10-489-273-4	Sequence 4, Appli
	12	60	63.2	325	16	US-10-262-473-15	Sequence 15, Appl
	13	58	61.1	57	17	US-10-621-684-1	Sequence 1, Appli
	14	58	61.1	57	17	US-10-621-684-4	Sequence 4, Appli
	15	58	61.1	57	20	US-10-775-481A-1	Sequence 1, Appli
	16	58	61.1	57	20	US-10-775-481A-4	Sequence 4, Appli
	17	58	61.1	69	20	US-10-766-735-64	Sequence 64, Appl
c	18	58	61.1	69	20	US-10-766-735-65	Sequence 65, Appl
	19	58	61.1	69	21	US-10-796-719-64	Sequence 64, Appl
c	20	58	61.1	69	21	US-10-796-719-65	Sequence 65, Appl
	21	58	61.1	497	21	US-10-696-639-2593	Sequence 2593, Ap
	22	56	58.9	65	10	US-09-908-975-3802	Sequence 3802, Ap
	23	56	58.9	367	16	US-10-262-473-13	Sequence 13, Appl
	24	56	58.9	409	16	US-10-262-473-11	Sequence 11, Appl
c	25	56	58.9	518	21	US-10-696-639-2594	Sequence 2594, Ap
	26	56	58.9	567	18	US-10-152-319A-1607	Sequence 1607, Ap
	27	56	58.9	571	10	US-09-873-367C-174	Sequence 174, App
	28	56	58.9	571	20	US-10-335-053-44	Sequence 44, Appl
	29	56	58.9	571	21	US-10-843-641A-174	Sequence 174, App
	30	56	58.9	650	14	US-10-158-646-41	Sequence 41, Appl
	31	56	58.9	655	9	US-09-981-353-60	Sequence 60, Appl
	32	56	58.9	655	15	US-10-235-994-21	Sequence 21, Appl
c	33	54	56.8	1603	18	US-10-424-599-44415	Sequence 44415, A
c	34	53	55.8	94720	18	US-10-052-482-160	Sequence 160, App
c	35	52.5	55.3	935	20	US-10-425-115-21919	Sequence 21919, A
c	36	52	54.7	252907	20	US-10-417-375-66	Sequence 66, Appl
	37	51	53.7	663	19	US-10-767-701-25585	Sequence 25585, A
c	38	51	53.7	1689	20	US-10-425-115-105712	Sequence 105712,
c	39	51	53.7	157090	19	US-10-672-764A-34	Sequence 34, Appl
c	40	51	53.7	495635	22	US-10-737-082-12	Sequence 12, Appl
c	41	51	53.7	495635	22	US-10-765-790-12	Sequence 12, Appl
c	42	51	53.7	705636	22	US-10-737-082-30	Sequence 30, Appl
c	43	51	53.7	705636	22	US-10-765-790-30	Sequence 30, Appl
	44	50	52.6	440	13	US-10-027-632-278769	Sequence 278769,
	45	50	52.6	440	17	US-10-027-632-278769	Sequence 278769,

ALIGNMENTS

RESULT 1
US-10-335-053-281
; Sequence 281, Application US/10335053
; Publication No. US20040241653A1
; GENERAL INFORMATION:
; APPLICANT: Quark Biotech, Inc.
; TITLE OF INVENTION: Methods for identifying marker genes for cancer
; FILE REFERENCE: 68733-A; 070/US1
; CURRENT APPLICATION NUMBER: US/10/335,053
; CURRENT FILING DATE: 2003-03-27
; PRIOR APPLICATION NUMBER: 60/345,317
; PRIOR FILING DATE: 2001-12-31
; NUMBER OF SEQ ID NOS: 319
; SOFTWARE: PatentIn version 3.2
; SEQ ID NO 281
; LENGTH: 596

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;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-10-335-053-281

Alignment Scores:
Pred. No.:              5.34e-05        Length:         596
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     20              Gaps:           0

US-10-107-814-20 (1-16) x US-10-335-053-281 (1-596)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        318 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 365

RESULT 2
US-10-737-082-6
; Sequence 6, Application US/10737082
; Publication No. US20050130170A1
; GENERAL INFORMATION:
;  APPLICANT: Bayer Healthcare LLC
;  APPLICANT:  Beard, Chris
;  APPLICANT:  Burgess, Chris
;  APPLICANT:  Gannon, Allison
;  APPLICANT:  Harvey, Jeanne
;  APPLICANT:  Lechner, John F.
;  APPLICANT:  Li, Zheng
;  TITLE OF INVENTION: Identification and Verification of Methylation Marker Sequences
;  FILE REFERENCE: 1657/2032
;  CURRENT APPLICATION NUMBER: US/10/737,082
;  CURRENT FILING DATE:  2003-12-16
;  PRIOR APPLICATION NUMBER: US 10/737,082
;  PRIOR FILING DATE: 2003-12-16
;  NUMBER OF SEQ ID NOS: 300
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 6
;   LENGTH: 3404
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-10-737-082-6

Alignment Scores:
Pred. No.:              0.000379        Length:         3404
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     22              Gaps:           0

US-10-107-814-20 (1-16) x US-10-737-082-6 (1-3404)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db       3126 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 3173

RESULT 3
US-10-765-790-6
; Sequence 6, Application US/10765790
; Publication No. US20050130172A1
; GENERAL INFORMATION:
;  APPLICANT: Bayer Healthcare LLC
;  APPLICANT:  Beard, Chris
;  APPLICANT:  Burgess, Chris
;  APPLICANT:  Gannon, Allison
;  APPLICANT:  Harvey, Jeanne
;  APPLICANT:  Lechner, John F.
;  APPLICANT:  Li, Zheng
;  TITLE OF INVENTION: Identification and Verification of Methylation Marker Sequences
;  FILE REFERENCE: 1657/2035
;  CURRENT APPLICATION NUMBER: US/10/765,790
;  CURRENT FILING DATE:  2004-01-27
;  PRIOR APPLICATION NUMBER: US 10/737,082
;  PRIOR FILING DATE: 2003-12-16
;  NUMBER OF SEQ ID NOS: 300
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 6
;   LENGTH: 3404
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-10-765-790-6

Alignment Scores:
Pred. No.:              0.000379        Length:         3404
Score:                  92.00           Matches:        15
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  93.75%          Mismatches:     0
Query Match:            96.84%          Indels:         0
DB:                     22              Gaps:           0

US-10-107-814-20 (1-16) x US-10-765-790-6 (1-3404)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db       3126 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 3173

RESULT 4
US-09-917-800A-1700
; Sequence 1700, Application US/09917800A
; Patent No. US20020119462A1
; GENERAL INFORMATION:
;  APPLICANT: Mendrick, Donna
;  APPLICANT:  Porter, Mark
;  APPLICANT:  Johnson, Kory
;  APPLICANT:  Castle, Arthur
;  APPLICANT:  Elashoff, Michael
;  APPLICANT:  Gene Logic, Inc.
;  TITLE OF INVENTION: Molecular Toxicology Modeling
;  FILE REFERENCE: 44921-5038-US
;  CURRENT APPLICATION NUMBER: US/09/917,800A
;  CURRENT FILING DATE:  2001-07-31
;  PRIOR APPLICATION NUMBER: US 60/222,040
;  PRIOR FILING DATE: 2000-07-31
;  PRIOR APPLICATION NUMBER: US 60/222,880
;  PRIOR FILING DATE: 2000-11-02
;  PRIOR APPLICATION NUMBER: US 60/290,029
;  PRIOR FILING DATE: 2001-05-11
;  PRIOR APPLICATION NUMBER: US 60/290,645
;  PRIOR FILING DATE: 2001-05-15
;  PRIOR APPLICATION NUMBER: US 60/292,336
;  PRIOR FILING DATE: 2001-05-22
;  PRIOR APPLICATION NUMBER: US 60/295,798
;  PRIOR FILING DATE: 2001-06-06
;  PRIOR APPLICATION NUMBER: US 60/297,457
;  PRIOR FILING DATE: 2001-06-13
;  PRIOR APPLICATION NUMBER: US 60/298,884
;  PRIOR FILING DATE: 2001-06-19
;  PRIOR APPLICATION NUMBER: US 60/303,459
;  PRIOR FILING DATE: 2001-07-09
;  NUMBER OF SEQ ID NOS: 1740
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 1700
;   LENGTH: 651
;   TYPE: DNA
;   ORGANISM: Rattus norvegicus
;   FEATURE:
;   OTHER INFORMATION: Genbank Accession No. US20020119462A1 NM_022284
US-09-917-800A-1700

Alignment Scores:
Pred. No.:              0.00106         Length:         651
Score:                  84.00           Matches:        13
Percent Similarity:     100.00%         Conservative:   1
Best Local Similarity:  92.86%          Mismatches:     0
```

Pg.267

Query Match: 88.42% Indels: 0
DB: 9 Gaps: 0

US-10-107-814-20 (1-16) x US-09-917-800A-1700 (1-651)

```
Qy          2 AspGluCysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||||||||:::||||||||||||||||||||
Db        440 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 481
```

RESULT 5
US-10-766-735-62
; Sequence 62, Application US/10766735
; Publication No. US20040266989A1
; GENERAL INFORMATION:
; APPLICANT: Currie, Mark G.
; APPLICANT: Mahajan-Miklos, Shalina
; TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR THE
; TITLE OF INVENTION: TREATMENT OF GASTROINTESTINAL DISORDERS
; FILE REFERENCE: 14184-039001
; CURRENT APPLICATION NUMBER: US/10/766,735
; CURRENT FILING DATE: 2004-01-28
; PRIOR APPLICATION NUMBER: US 60/443,098
; PRIOR FILING DATE: 2003-01-28
; PRIOR APPLICATION NUMBER: US 60/471,288
; PRIOR FILING DATE: 2003-05-15
; PRIOR APPLICATION NUMBER: US 60/519,460
; PRIOR FILING DATE: 2003-11-12
; NUMBER OF SEQ ID NOS: 124
; SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 62
; LENGTH: 69
; TYPE: DNA
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Synthetically generated oligonucleotide
US-10-766-735-62

Alignment Scores:
Pred. No.: 0.164 Length: 69
Score: 63.00 Matches: 10
Percent Similarity: 83.33% Conservative: 0
Best Local Similarity: 83.33% Mismatches: 2
Query Match: 66.32% Indels: 0
DB: 20 Gaps: 0

US-10-107-814-20 (1-16) x US-10-766-735-62 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         24 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 59
```

RESULT 6
US-10-766-735-63/c
; Sequence 63, Application US/10766735
; Publication No. US20040266989A1
; GENERAL INFORMATION:
; APPLICANT: Currie, Mark G.
; APPLICANT: Mahajan-Miklos, Shalina
; TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR THE
; TITLE OF INVENTION: TREATMENT OF GASTROINTESTINAL DISORDERS
; FILE REFERENCE: 14184-039001
; CURRENT APPLICATION NUMBER: US/10/766,735
; CURRENT FILING DATE: 2004-01-28
; PRIOR APPLICATION NUMBER: US 60/443,098
; PRIOR FILING DATE: 2003-01-28
; PRIOR APPLICATION NUMBER: US 60/471,288
; PRIOR FILING DATE: 2003-05-15
; PRIOR APPLICATION NUMBER: US 60/519,460
; PRIOR FILING DATE: 2003-11-12
; NUMBER OF SEQ ID NOS: 124
; SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 63
; LENGTH: 69
; TYPE: DNA
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Synthetically generated oligonucleotide
US-10-766-735-63

Alignment Scores:
Pred. No.: 0.164 Length: 69
Score: 63.00 Matches: 10
Percent Similarity: 83.33% Conservative: 0
Best Local Similarity: 83.33% Mismatches: 2
Query Match: 66.32% Indels: 0
DB: 20 Gaps: 0

US-10-107-814-20 (1-16) x US-10-766-735-63 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         50 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 15
```

RESULT 7
US-10-796-719-62
; Sequence 62, Application US/10796719
; Publication No. US20050020811A1
; GENERAL INFORMATION:
; APPLICANT: Currie, Mark G.
; APPLICANT: Mahajan-Miklos, Shalina
; TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR THE
; TITLE OF INVENTION: TREATMENT OF GASTROINTESTINAL DISORDERS
; FILE REFERENCE: 14184-043001
; CURRENT APPLICATION NUMBER: US/10/796,719
; CURRENT FILING DATE: 2004-03-09
; PRIOR APPLICATION NUMBER: US 10/766,735
; PRIOR FILING DATE: 2004-01-28
; PRIOR APPLICATION NUMBER: US 60/443,098
; PRIOR FILING DATE: 2003-01-28
; PRIOR APPLICATION NUMBER: US 60/471,288
; PRIOR FILING DATE: 2003-05-15
; PRIOR APPLICATION NUMBER: US 60/519,460
; PRIOR FILING DATE: 2003-11-12
; NUMBER OF SEQ ID NOS: 149
; SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 62
; LENGTH: 69
; TYPE: DNA
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Synthetically generated oligonucleotide
US-10-796-719-62

Alignment Scores:
Pred. No.: 0.164 Length: 69
Score: 63.00 Matches: 10
Percent Similarity: 83.33% Conservative: 0
Best Local Similarity: 83.33% Mismatches: 2
Query Match: 66.32% Indels: 0
DB: 21 Gaps: 0

US-10-107-814-20 (1-16) x US-10-796-719-62 (1-69)

```
Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         24 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 59
```

RESULT 8
US-10-796-719-63/c
; Sequence 63, Application US/10796719
; Publication No. US20050020811A1
; GENERAL INFORMATION:
; APPLICANT: Currie, Mark G.
; APPLICANT: Mahajan-Miklos, Shalina
; TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR THE
; TITLE OF INVENTION: TREATMENT OF GASTROINTESTINAL DISORDERS

```
;  FILE REFERENCE: 14184-043001
;  CURRENT APPLICATION NUMBER: US/10/796,719
;  CURRENT FILING DATE:  2004-03-09
;  PRIOR APPLICATION NUMBER: US 10/766,735
;  PRIOR FILING DATE: 2004-01-28
;  PRIOR APPLICATION NUMBER: US 60/443,098
;  PRIOR FILING DATE: 2003-01-28
;  PRIOR APPLICATION NUMBER: US 60/471,288
;  PRIOR FILING DATE: 2003-05-15
;  PRIOR APPLICATION NUMBER: US 60/519,460
;  PRIOR FILING DATE: 2003-11-12
;  NUMBER OF SEQ ID NOS: 149
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 63
;   LENGTH: 69
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Synthetically generated oligonucleotide
US-10-796-719-63

Alignment Scores:
Pred. No.:              0.164          Length:         69
Score:                  63.00          Matches:        10
Percent Similarity:     83.33%         Conservative:   0
Best Local Similarity:  83.33%         Mismatches:     2
Query Match:            66.32%         Indels:         0
DB:                     21             Gaps:           0

US-10-107-814-20 (1-16) x US-10-796-719-63 (1-69)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db         50 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 15

RESULT 9
US-10-425-821-88
; Sequence 88, Application US/10425821
; Publication No. US20040219530A1
; GENERAL INFORMATION:
;  APPLICANT: BROUSSEAU, Roland
;  APPLICANT:  HAREL, Jos,e
;  APPLICANT:  BEKAL, Sadjia
;  TITLE OF INVENTION: ARRAY AND USES THEREOF
;  FILE REFERENCE: 86369-3
;  CURRENT APPLICATION NUMBER: US/10/425,821
;  CURRENT FILING DATE:  2003-04-30
;  NUMBER OF SEQ ID NOS: 176
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 88
;   LENGTH: 214
;   TYPE: DNA
;   ORGANISM: Escherichia coli
US-10-425-821-88

Alignment Scores:
Pred. No.:              0.587          Length:         214
Score:                  63.00          Matches:        10
Percent Similarity:     83.33%         Conservative:   0
Best Local Similarity:  83.33%         Mismatches:     2
Query Match:            66.32%         Indels:         0
DB:                     20             Gaps:           0

US-10-107-814-20 (1-16) x US-10-425-821-88 (1-214)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db        175 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 210

RESULT 10
US-10-489-273-1
; Sequence 1, Application US/10489273
; Publication No. US20050054075A1
; GENERAL INFORMATION:
;  APPLICANT: Turner, Arthur Keith
;  APPLICANT:  Greenwood, Judith
;  APPLICANT:  Stephens, Jonathan Clive
;  APPLICANT:  Beavis, Juliet Claire
;  APPLICANT:  Darsley, Michael James
;  TITLE OF INVENTION: Attenuated Bacteria Useful in Vaccines
;  FILE REFERENCE: 117-499 / N83542B
;  CURRENT APPLICATION NUMBER: US/10/489,273
;  CURRENT FILING DATE:  2004-03-11
;  PRIOR APPLICATION NUMBER: PCT/GB02/04164
;  PRIOR FILING DATE: 2002-09-11
;  PRIOR APPLICATION NUMBER: GB 0121998.9
;  PRIOR FILING DATE: 2001-09-11
;  NUMBER OF SEQ ID NOS: 103
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 1
;   LENGTH: 950
;   TYPE: DNA
;   ORGANISM: Escherichia coli
US-10-489-273-1

Alignment Scores:
Pred. No.:              3.15           Length:         950
Score:                  63.00          Matches:        10
Percent Similarity:     83.33%         Conservative:   0
Best Local Similarity:  83.33%         Mismatches:     2
Query Match:            66.32%         Indels:         0
DB:                     21             Gaps:           0

US-10-107-814-20 (1-16) x US-10-489-273-1 (1-950)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||||||||||||
Db        324 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 359

RESULT 11
US-10-489-273-4
; Sequence 4, Application US/10489273
; Publication No. US20050054075A1
; GENERAL INFORMATION:
;  APPLICANT: Turner, Arthur Keith
;  APPLICANT:  Greenwood, Judith
;  APPLICANT:  Stephens, Jonathan Clive
;  APPLICANT:  Beavis, Juliet Claire
;  APPLICANT:  Darsley, Michael James
;  TITLE OF INVENTION: Attenuated Bacteria Useful in Vaccines
;  FILE REFERENCE: 117-499 / N83542B
;  CURRENT APPLICATION NUMBER: US/10/489,273
;  CURRENT FILING DATE:  2004-03-11
;  PRIOR APPLICATION NUMBER: PCT/GB02/04164
;  PRIOR FILING DATE: 2002-09-11
;  PRIOR APPLICATION NUMBER: GB 0121998.9
;  PRIOR FILING DATE: 2001-09-11
;  NUMBER OF SEQ ID NOS: 103
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 4
;   LENGTH: 1183
;   TYPE: DNA
;   ORGANISM: Escherichia coli
US-10-489-273-4

Alignment Scores:
Pred. No.:              4.03           Length:         1183
Score:                  63.00          Matches:        10
Percent Similarity:     83.33%         Conservative:   0
Best Local Similarity:  83.33%         Mismatches:     2
Query Match:            66.32%         Indels:         0
DB:                     21             Gaps:           0

US-10-107-814-20 (1-16) x US-10-489-273-4 (1-1183)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
```

```
                ||||||||||||   |||   ||||||||||||||||
Db        248 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 283

RESULT 12
US-10-262-473-15
; Sequence 15, Application US/10262473
; Publication No. US20030199442A1
; GENERAL INFORMATION:
;  APPLICANT: Alsobrook, John,
;  APPLICANT:  Burgess, Catherine,
;  APPLICANT:  Gorman, Linda,
;  APPLICANT:  Guo, Xiaojia,
;  APPLICANT:  Lepley, Denise,
;  APPLICANT:  Patturajan, Meera,
;  APPLICANT:  Rastelli, Luca,
;  APPLICANT:  Reiger, Daniel,
;  APPLICANT:  Spytek, Kimberly,
;  APPLICANT:  Zhong, Mei
;  TITLE OF INVENTION: THERAPEUTIC POLYPEPTIDES, NUCLEIC ACIDS ENCODING SAME, AND METHOD
;  FILE REFERENCE: 21402-462B
;  CURRENT APPLICATION NUMBER: US/10/262,473
;  CURRENT FILING DATE:  2003-01-28
;  PRIOR APPLICATION NUMBER: 60/327,917
;  PRIOR FILING DATE: 2001-10-09
;  PRIOR APPLICATION NUMBER: 60/328,029
;  PRIOR FILING DATE: 2001-10-09
;  PRIOR APPLICATION NUMBER: 60/328,056
;  PRIOR FILING DATE: 2001-10-09
;  PRIOR APPLICATION NUMBER: 60/349,575
;  PRIOR FILING DATE: 2001-10-29
;  PRIOR APPLICATION NUMBER: 60/381,038
;  PRIOR FILING DATE: 2002-05-16
;  NUMBER OF SEQ ID NOS: 22
;  SOFTWARE: CuraSeqList version 0.1
; SEQ ID NO 15
;   LENGTH: 325
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (2)..(325)
US-10-262-473-15

Alignment Scores:
Pred. No.:              2.77          Length:          325
Score:                  60.00         Matches:         9
Percent Similarity:     76.92%        Conservative:    1
Best Local Similarity:  69.23%        Mismatches:      3
Query Match:            63.16%        Indels:          0
DB:                     16            Gaps:            0

US-10-107-814-20 (1-16) x US-10-262-473-15 (1-325)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||         ||||||||||||||||||
Db        281 TGTGAAATCTGTGCCTACGCTGCCTGTACCGGATGCCTC 319

RESULT 13
US-10-621-684-1
; Sequence 1, Application US/10621684
; Publication No. US20040029182A1
;   GENERAL INFORMATION:
;        APPLICANT: Waldman, Scott A.
;        TITLE OF INVENTION: ST Receptor Binding Compounds and
;                            Methods of Using the Same
;        NUMBER OF SEQUENCES: 56
;        CORRESPONDENCE ADDRESS:
;             ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. US20040029182A1ris
;             STREET: One Liberty Place, 46th Floor
;             CITY: Philadelphia
;             STATE: Pennsylvania
;             COUNTRY: USA
;             ZIP: 19103
;        COMPUTER READABLE FORM:
;             MEDIUM TYPE: Floppy disk
;             COMPUTER: IBM PC compatible
;             OPERATING SYSTEM: Windows
;             SOFTWARE: WordPerfect 6.1
;        CURRENT APPLICATION DATA:
;             APPLICATION NUMBER: US/10/621,684
;             FILING DATE: 17-Jul-2003
;             CLASSIFICATION: 435
;        PRIOR APPLICATION DATA:
;             APPLICATION NUMBER: US/08/583,447A
;             FILING DATE: 05-JAN-1996
;             APPLICATION NUMBER: US 08/141,892
;             FILING DATE: 26-OCT-1993
;        ATTORNEY/AGENT INFORMATION:
;             NAME: DeLuca, Mark
;             REGISTRATION NUMBER: 33,229
;             REFERENCE/DOCKET NUMBER: TJU-1702
;        TELECOMMUNICATION INFORMATION:
;             TELEPHONE: 215-568-3100
;             TELEFAX: 215-568-3439
;   INFORMATION FOR SEQ ID NO: 1:
;        SEQUENCE CHARACTERISTICS:
;             LENGTH: 57 base pairs
;             TYPE: nucleic acid
;             STRANDEDNESS: double
;             TOPOLOGY: both
;        MOLECULE TYPE: cDNA
;        FEATURE:
;             NAME/KEY:  CDS
;             LOCATION:  1..57
;        SEQUENCE DESCRIPTION: SEQ ID NO: 1:
US-10-621-684-1

Alignment Scores:
Pred. No.:              0.804         Length:          57
Score:                  58.00         Matches:         9
Percent Similarity:     75.00%        Conservative:    0
Best Local Similarity:  75.00%        Mismatches:      3
Query Match:            61.05%        Indels:          0
DB:                     17            Gaps:            0

US-10-107-814-20 (1-16) x US-10-621-684-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54

RESULT 14
US-10-621-684-4
; Sequence 4, Application US/10621684
; Publication No. US20040029182A1
;   GENERAL INFORMATION:
;        APPLICANT: Waldman, Scott A.
;        TITLE OF INVENTION: ST Receptor Binding Compounds and
;                            Methods of Using the Same
;        NUMBER OF SEQUENCES: 56
;        CORRESPONDENCE ADDRESS:
;             ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. US20040029182A1ris
;             STREET: One Liberty Place, 46th Floor
;             CITY: Philadelphia
;             STATE: Pennsylvania
;             COUNTRY: USA
;             ZIP: 19103
;        COMPUTER READABLE FORM:
;             MEDIUM TYPE: Floppy disk
;             COMPUTER: IBM PC compatible
;             OPERATING SYSTEM: Windows
;             SOFTWARE: WordPerfect 6.1
;        CURRENT APPLICATION DATA:
;             APPLICATION NUMBER: US/10/621,684
;             FILING DATE: 17-Jul-2003
;             CLASSIFICATION: 435
```

```
;        PRIOR APPLICATION DATA:
;             APPLICATION NUMBER: US/08/583,447A
;             FILING DATE: 05-JAN-1996
;             APPLICATION NUMBER: US 08/141,892
;             FILING DATE: 26-OCT-1993
;        ATTORNEY/AGENT INFORMATION:
;             NAME: DeLuca, Mark
;             REGISTRATION NUMBER: 33,229
;             REFERENCE/DOCKET NUMBER: TJU-1702
;        TELECOMMUNICATION INFORMATION:
;             TELEPHONE: 215-568-3100
;             TELEFAX: 215-568-3439
;   INFORMATION FOR SEQ ID NO: 4:
;        SEQUENCE CHARACTERISTICS:
;             LENGTH: 57 base pairs
;             TYPE: nucleic acid
;             STRANDEDNESS: double
;             TOPOLOGY: both
;        MOLECULE TYPE: cDNA
;        FEATURE:
;             NAME/KEY:  CDS
;             LOCATION:  1..57
;        SEQUENCE DESCRIPTION: SEQ ID NO: 4:
US-10-621-684-4

Alignment Scores:
Pred. No.:              0.804          Length:        57
Score:                  58.00          Matches:       9
Percent Similarity:     75.00%         Conservative:  0
Best Local Similarity:  75.00%         Mismatches:    3
Query Match:            61.05%         Indels:        0
DB:                     17             Gaps:          0

US-10-107-814-20 (1-16) x US-10-621-684-4 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54

RESULT 15
US-10-775-481A-1
; Sequence 1, Application US/10775481A
; Publication No. US20040258687A1
; GENERAL INFORMATION:
;  APPLICANT: Waldman, Scott A.
;  APPLICANT:  Pitari, Giovanni Mario
;  APPLICANT:  Park, Jason
;  APPLICANT:  Schulz, Stephanie
;  APPLICANT:  Wolfe, Henry R.
;  APPLICANT:  Lubbe, Wilhelm
;  TITLE OF INVENTION: The Use Of GCC Ligands
;  FILE REFERENCE: 08321-0168 US1
;  CURRENT APPLICATION NUMBER: US/10/775,481A
;  CURRENT FILING DATE:  2004-02-10
;  PRIOR APPLICATION NUMBER: US 60/446,730
;  PRIOR FILING DATE: 2003-02-10
;  NUMBER OF SEQ ID NOS: 56
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 1
;   LENGTH: 57
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: encodes heat stable toxin peptide of SEQ ID NO: 2
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (1)...(57)
US-10-775-481A-1

Alignment Scores:
Pred. No.:              0.804          Length:        57
Score:                  58.00          Matches:       9
Percent Similarity:     75.00%         Conservative:  0
Best Local Similarity:  75.00%         Mismatches:    3
Query Match:            61.05%         Indels:        0
DB:                     20             Gaps:          0

US-10-107-814-20 (1-16) x US-10-775-481A-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54


Search completed: August 28, 2005, 15:17:07
Job time : 454 secs
```

AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

43569 7590 11/01/2005

MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/01/2005

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943	9117

TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	02/01/2006

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 07/05) Approved for use through 04/30/2007.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

or Fax **(571) 273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

43569 7590 11/01/2005

MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON, DC 20006

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943	9117

TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$1700	02/01/2006

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAWLINGS, STEPHEN L	1643	530-317000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____ 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943	9117

43569 7590 11/01/2005

MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/01/2005

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 479 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 479 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 07/05) Approved for use through 04/30/2007.

Notice of Allowability	Application No.	Applicant(s)	
	10/107,814	SHAILUBHAI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *15 August 2005*.

2. ☒ The allowed claim(s) is/are *1,20-23 and 26*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☒ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 20050815
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20051024* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Gregory J. Sieczkiewicz on October 16, 2005.

2. The application has been amended as follows:

In the claims:

Claims 20-23 have been amended as follows:

20. (Currently amended) A ~~pharmaceutical~~ composition in unit dose comprising a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEO ID NO: 20 ~~present in a therapeutically effective amount~~.

21. (Currently amended) A ~~pharmaceutical~~ composition in unit dose form comprising: a) a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO: 20; and b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor, an anti-inflammatory agent, an antiviral agent and an anticancer agent~~; wherein said guanylate cyclase receptor agonist and said compound are each present in a therapeutically effective amount~~.

22. (Currently amended) The ~~pharmaceutical~~ composition of either claim 20 or 21, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution ~~or~~ and an inhalation formulation.

23. (Currently amended) The ~~pharmaceutical~~ composition of either claim 20 ~~nor~~ or 21, further comprising one or more excipients.

In the specification:

The paragraph beginning at page 23, line 30 has been replaced with the following:

12. Basoglu, et al., in: Proceedings of the Second FEPS Congress, June 29-Jul. 4, 1999, Prague, Czech Republic~~., http://1f2.cuni.cz/physiolres/feps/basoglu.htm~~.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the copy of the declaration filed August 1, 2002 is not legible; in particular, the signatures and hand-written dates have not been reproduced such that they may be read. Applicant's procurement and submission of a substitute copy of the declaration, which has been legibly reproduced, will prevent delay during the preparation of the published patent document.

Conclusion

4. Claims 1, 20-23, and 26 have been allowed and renumbered as claims 1-6, respectively.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
October 24, 2005

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/107,814	SHAILUBHAI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

All Participants: **Status of Application:** _____

(1) *Stephen L. Rawlings, Ph.D.*. (3) _____.

(2) *Gregory J. Sieczkiewicz*. (4) _____.

Date of Interview: *16 October 2005* **Time:** _____

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description:

Part I.

Rejection(s) discussed:

Claims discussed:
1, 20-23, and 26

Prior art documents discussed:

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Examiner/SPE Signature) (Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed: The Examiner telephoned Mr. Sieczkiewicz to propose an examiner's amendment in which claims 20-23 would be amended to delete "pharmaceutical", claim 20 would be further amended to delete "present in a therapeutically effective amount", claim 21 would be further amended to delete "; wherein said guanylate cyclase receptor agonist and said compound are each present in a therapeutically effective amount, claim 22 would be further amended to recite "and an" in place of "or" between "solution" and "inhalation formulation", and claim 23 would be further amended to recite "or" in place of "nor". Furthermore, the specification would be amended to delete ", http://1f2.cuni.cz/physiores/feps/basoglu.htm". Mr. Sieczkiewicz authorized entry of the proposed examiner's amendment. .

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

OIPE
AUG 15 2005
PATENT & TRADEMARK OFFICE

Please type a plus sign (+) in this box [+]

PTO/SB (12-97)
Approved for use through 9/30/00. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Modified Form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Application Number	10/107,814
Filing Date	March 28, 2002
First Named Inventor	Shailubhai
Group Art Unit	1642
Examiner Name	Stephen L. Rawlings
Attorney Docket Number	33357-503

U.S. PATENT DOCUMENTS

Exam Initials	Cite No.	U.S. Patent Document No.	Issue Date	Name of Patentee(s) or Applicant(s)	Class	Sub Class	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

Exam Initials	Cite No.	Foreign Patent Document Office	Number	Name of Patentee(s) or Applicant(s)	Date of Publication	Translation Yes	No

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Exam Initials	Cite No.	Name of Author, Title (when appropriate), Publication, Volume, Page(s), Date, Etc.
SR	ZR	Sindice, et al., Journal of Biological Chemistry, 277:17758-17764 (2002).

Examiner Signature		Date Considered	10/20/05

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

TRA 2064031v1

Search Notes (continued)	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/107,814	SHAILUBHAI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**10**	**10/24/2005**	**SR**
514	13	10/24/2005	SR

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/107,814	SHAILUBHAI ET AL.	
Examiner	**Art Unit**	
Stephen L. Rawlings, Ph.D.	1643	

SEARCHED			
Class	Subclass	Date	Examiner
updated	updated	10/24/2005	SR
530	317	10/24/2005	SR
530	300	10/24/2005	SR
530	326	10/24/2005	SR
514	10	10/24/2005	SR
514	13	10/24/2005	SR

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
530	**317**	**10/24/2005**	**SR**
530	300	10/24/2005	SR
530	326	10/24/2005	SR
sequence search: SEQ ID NO: 20 (interference databases)		9/1/2005	SR

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
updated sequence search: SEQ ID NO: 20 (all commercial, issued, published and interference databases)	9/1/2005	SR
updated WEST (PGPUB, USPT, EPOA, JPOA, DWPI); PALM-EXPO: Shailubhai K; Nikiforovich G; Jacob GS	10/24/2005	SR
updated 60/348,646	10/24/2005	SR
updated MEDLINE; WEST (PGPUB, USPT, EPOA, JPOA, DWPI): Shailubhai K; Nikiforovich G; Jacob GS; uroguanylin; variant; mutant	10/24/2005	SR
Conferred with L. Helms re. claim interpretation	10/24/2005	SR

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination
	10/107,814	SHAILUBHAI ET AL.
	Examiner	Art Unit
	Stephen L. Rawlings, Ph.D.	1643

ISSUE CLASSIFICATION

ORIGINAL					CROSS REFERENCE(S)							
CLASS				SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
530				317	530	300	326					
INTERNATIONAL CLASSIFICATION					514	10	13					
A	6	1	K	38/12								
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				/								
				/								
				/								

(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

10/24/05

Stephen L. Rawlings

(Primary Examiner) (Date)

Total Claims Allowed: 6

O.G. Print Claim(s)	O.G. Print Fig.
1	None

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
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	7		37		67		97		127		157		187
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	29		59		89		119		149		179		209
	30		60		90		120		150		180		210

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/107,814	SHAILUBHAI ET AL.
Examiner	**Art Unit**
Stephen L. Rawlings, Ph.D.	1643

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date								
Final	Original	10/24/05								
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UNITED STATES PATENT AND TRADEMARK OFFICE

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Bib Data Sheet

CONFIRMATION NO. 9117

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/107,814	03/28/2002 RULE	514	1643	P 0284943

APPLICANTS

Kunwar Shailubhai, Blue Bell, PA;

Gregory Nikiforovich, St. Louis, MO;
Gary S. Jacob, Creve Coeur, MO;

** CONTINUING DATA **********

This appln claims benefit of ~~60/279,438 03/29/2001~~
~~and claims benefit of 60/300,850 06/27/2001~~ SR
~~and claims benefit of 60/307,358 07/25/2001~~
~~and claims benefit of 60/279,437 03/29/2001~~
~~and claims benefit of 60/303,806 07/10/2001~~
~~and claims benefit of~~ 60/348,646 01/17/2002

SR

** FOREIGN APPLICATIONS **********

SR

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 05/02/2002

Foreign Priority claimed ☐ yes ☒ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged Examiner's Signature Initials SR	STATE OR COUNTRY PA	SHEETS DRAWING 0	TOTAL CLAIMS 27	INDEPENDENT CLAIMS 12

ADDRESS
43569
MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON , DC
20006

TITLE
Guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis

☐ All Fees

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Bib Data Sheet

CONFIRMATION NO. 9117

SERIAL NUMBER	FILING OR 371(c) DATE / RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/107,814	03/28/2002	514	1643	P 0284943

APPLICANTS

Kunwar Shailubhai, Blue Bell, PA;
Gregory Nikiforovich, St. Louis, MO;
Gary S. Jacob, Creve Coeur, MO;

**** CONTINUING DATA **********

This appln claims benefit of 60/348,646 01/17/2002

**** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED **

05/02/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	PA	0	27	12
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged _____ Examiner's Signature _____ Initials				

ADDRESS

43569

TITLE

Guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis

FILING FEE RECEIVED		
2158	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

01-18-06

Express Mail Label No. EV695511017US

PART B - FEE(S) TRANSMITTAL

OIPE JAN 13 2006 PATENT & TRADEMARK OFFICE

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

43569 7590 11/01/2005

MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON, DC 20006

01/18/2006 KBETEMA2 00000056 10107814

01 FC:2501 700.00 OP
02 FC:1504 300.00 OP

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943	9117

TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	~~NO~~ YES	~~$1400~~ 700	$300	~~$1700~~ 1000	02/01/2006

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAWLINGS, STEPHEN L	1643	530-317000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Mintz, Levin, Cohn, Ferris Glovsky and Popeo, P.C.
2 Ivor R. Elrifi
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: CALLISTO PHARMACEUTICALS
(B) RESIDENCE: (CITY and STATE OR COUNTRY): NEW YORK, NY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):
☒ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized by charge [redacted] additional fee(s), or credit any overpayment, to Deposit Account Number 50-0311 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☒ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date January 13, 2006

Typed or printed name Gregory J. Sieczkiewicz Registration No. 48,223

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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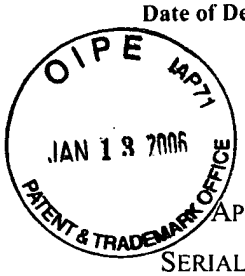
Date of Deposit: January 13, 2006

Attorney Docket No. 33357-503



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Shailubhai *et al.*
SERIAL NUMBER: 10/107,814 EXAMINER : Stephen L. Rawlings
FILING DATE: March 28, 2002 ART UNIT 1643
FOR: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Enclosed herewith for filing in the above-identified application please find the following documents:

1. Response to Notice of Allowance and Fees Due (1 page);
2. Form PTOL-85, Part B (1 page) (in duplicate);
3. Check No. 21815 in the amount of $1000;
4. Replacement Declaration and Power of Attorney form (2 pages); and
5. Return Postcard

The Commissioner is hereby authorized to charge payment of any additional fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311, (Reference No. 33357-503). A duplicate copy of this transmittal letter is enclosed.

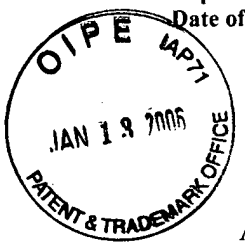
Respectfully submitted,

Ivor R. Elrifi (Reg. No. 39,529)
Gregory J. Sieczkiewicz (Reg. No. 48,223)
Attorneys for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623

Dated: January 13, 2006

TRA 2111645

Express Mail Label No. EV695511017US
Date of Deposit: January 13, 2006



Attorney Docket No. 33357-503

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Shailubhai *et al.*

SERIAL NUMBER: 10/107,814 EXAMINER : Stephen L. Rawlings

FILING DATE: March 28, 2002 ART UNIT 1643

FOR: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF ALLOWANCE AND FEES DUE

In response to the Notice of Allowance and Fee(s) Due, mailed November 1, 2005 the following is submitted herewith for filing in the above-referenced application: Form PTOL-85, Part B and Check No. 21815 in the amount of $1,000. Applicants hereby claim small entity status. In addition, Applicants submit herewith a replacement Declaration and Power of Attorney form in compliance with 37 CFR § 1.67(a).

Applicants believe no additional fees are due with this timely filing. However, the Commissioner is hereby authorized to charge any additional fees that may be due, or to credit any overpayment, to Account 50-0311, Ref. No. 33357-503. An extra copy of Part B of Form PTOL-85 is enclosed for this purpose.

Respectfully submitted,

Dated: January 13, 2006

Ivor R. Elrifi (Reg. No. 39,529)
Gregory J. Sieczkiewicz (Reg. No. 48,223)
Attorneys for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623

TRA 2111626

FOR UTILITY/DESIGN
CIP/PCT NATIONAL/PLANT
ORIGINAL/SUBSTITUTE/SUPPLEMENTAL
DECLARATIONS

OIPE IAP71
JAN 1 8 2006
PATENT & TRADEMARK OFFICE

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PW
FORM

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

the specification of which (CHECK applicable BOX(ES))

X BOX(ES) A. ☐ is attached hereto.
→ B. ☒ was filed on March 28, 2002 as U.S. Application No. 10/107,814
→ C. ☐ was filed as PCT International Application No. PCT/ / on

and (if applicable to U.S. or PCT application) was amended on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first Laid-open or Published	Date Patented or Granted	Priority NOT Claimed

If more prior foreign applications, X box *at bottom* and continue on attached page.

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C. 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status pending, abandoned, patented	Priority NOT Claimed
60/279,438	29/03/2001		
60/279,437	29/03/2001		
60/300,850	27/6/2001		
60/303,806	10/7/2001		
60/307,358	25/7/2001		
60/348,646	17/1/2002		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Winthrop LLP, Intellectual Property Group, telephone number (703) 905-2000 (to whom all communications are to be directed), and persons of that firm who are associated with USPTO Customer No. 909 (see below label) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete from that Customer No. names of persons no longer with their firm, to add new persons of their Firm to that Customer No., and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or an attorney of that Firm in writing to the contrary.

USE ONLY FOR
PILLSBURY WINTHROP

00909

(1) INVENTOR'S SIGNATURE: Date: 6/18/02

Name	Kunwar		SHAILUBHAI
	First	Middle Initial	Family Name
Residence	Blue Bell	PA	USA
	City	State/Foreign Country	Country of Citizenship
Mailing Address	600 Wick Lane, Blue Bell, PA, USA		
(include Zip Code)	19422		

(2) INVENTOR'S SIGNATURE: Date: 6/19/02

Name	Gregory		NIKIFOROVICH
	First	Middle Initial	Family Name
Residence	St. Louis	MO	USA
	City	State/Foreign Country	Country of Citizenship
Mailing Address	751 Aramis Drive, St. Louis, MO, USA		
(include Zip Code)	63141		

☒ FOR ADDITIONAL INVENTORS see attached page.
☐ See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. P284943

DECLARATION AND POWER OF ATTORNEY
(continued)
ADDITIONAL INVENTORS:

(3) INVENTOR'S SIGNATURE: [signature] Date: June 18, 2002

	Gary	S.	JACOB
	First	Middle Initial	Family Name
Residence	Creve Coeur	MO	USA
	City	State/Foreign Country	Country of Citizenship
Mailing Address	12541 Mason Forest Drive, Creve Coeur, MO, USA		
(include Zip Code)	63141		

(4) INVENTOR'S SIGNATURE: Date:

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(5) INVENTOR'S SIGNATURE: Date:

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(6) INVENTOR'S SIGNATURE: Date:

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(7) INVENTOR'S SIGNATURE: Date:

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(8) INVENTOR'S SIGNATURE: Date:

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(9) INVENTOR'S SIGNATURE: Date:

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

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Bib Data Sheet

CONFIRMATION NO. 9117

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/107,814	03/28/2002 RULE	530	1643	P 0284943

APPLICANTS

Kunwar Shailubhai, Blue Bell, PA;
Gregory Nikiforovich, St. Louis, MO;
Gary S. Jacob, Creve Coeur, MO;

**** CONTINUING DATA **********

This appln claims benefit of 60/348,646 01/17/2002

**** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 05/02/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	PA	0	27	12
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged _____ Examiner's Signature Initials				

ADDRESS

43569

TITLE

GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:
2458	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

10-03-07

DAC

IFW

Express Mail Label No.: EV 538966998 US
Date of Deposit: October 1, 2007

Attorney Docket No.: 33357-503

OIPE
OCT 0 1 2007
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Shailubhai, *et al.*		
PATENT NUMBER:	7,041,786	ISSUE DATE:	May 9, 2006
SERIAL NUMBER:	10/107,814	EXAMINER:	Stephen L. Rawlings
FILING DATE:	March 28, 2002	ART UNIT:	1643
FOR:	GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS		

Boston, Massachusetts
October 1, 2007

Mail Stop PETITIONS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL

Transmitted herewith for filing in the present application are the following documents:

1. Request for Certificate of Correction (2 pages);
2. Proposed Certificate of Correction (1 page, in duplicate);
3. Statement in Support of Request under 37 C.F.R. §3.81 (2 pages);
4. Copy of the Notice of Recordation of Assignment Document - Exhibit A (2 pages);
5. Copy of the executed Assignment Document to Synergy Pharmaceuticals Inc. - Exhibit B (2 pages);
6. Check No. 24706 in the amount of $100.00 (certificate of correction);
7. Check No. 24707 in the amount of $130.00 (processing fee);
8. Return postcard.

The Commissioner is hereby authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference No. 33357-503. A duplicate copy of this Transmittal is enclosed.

Respectfully submitted,

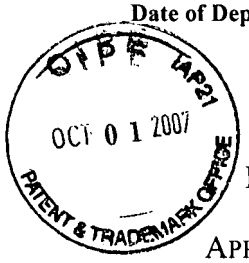
Ivor R. Elrifi, Reg. No. 39,529
Cynthia A. Kozakiewicz, Reg. No. 42,764
Attorneys for Applicants
Tel: (617) 542-6000
Fax: (617) 542-2241

Customer Number 30623

4155226v.1

Express Mail Label No.: EV 538966998 US
Date of Deposit: October 1, 2007

Attorney Docket No.: 33357-503



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Shailubhai, *et al.*		
PATENT NUMBER:	7,041,786	ISSUE DATE:	May 9, 2006
SERIAL NUMBER:	10/107,814	EXAMINER:	Stephen L. Rawlings
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Boston, Massachusetts
October 1, 2007

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P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION OF LETTERS PATENT

1. Attached, in duplicate, is Form PTO-1050, with at least one copy being suitable for printing.

2. The exact pages and line numbers of the corrections are:

   At Page 1, line 73, the Assignee should be: "Synergy Pharmaceuticals Inc." (US).

3. Please send the Certificate of Correction to:

Ivor R. Elrifi, Esq.
Attorney for Applicants
MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, MA 02111

10/04/2007 EAYALEW1 00000026 7041786
01 FC:1811 100.00 OP

REMARKS

Applicants request this Certificate of Correction to correct the assignee name. In accordance with 37 CFR 1.20(a), a check for $100.00 is enclosed herewith in payment of the Certificate of Correction. Should the Certificates Branch wish to discuss Applicant's request, the Certificates Branch is invited to telephone the undersigned attorneys at 617/542-6000.

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Cynthia A. Kozakiewicz, Reg. No. 42,764
Attorneys for Applicants
Tel: (617) 542-6000
Fax: (617) 542-2241

Customer Number 30623

4155226v.1

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.:	7,041,786
APPLICATION NO.:	10/107,814
ISSUE DATE:	May 9, 2006
INVENTOR(S):	Shailubhai, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1, line 73, the Assignee should be: "Synergy Pharmaceuticals Inc." (US).

MAILING ADDRESS OF SENDER:

Ivor R. Elrifi, Reg. No. 39,529
Cynthia A. Kozakiewicz, Reg. No. 42,764
Attorneys for Applicants
MINTZ LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.:	7,041,786
APPLICATION NO.:	10/107,814
ISSUE DATE:	May 9, 2006
INVENTOR(S):	Shailubhai, et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1, line 73, the Assignee should be: "Synergy Pharmaceuticals Inc." (US).

MAILING ADDRESS OF SENDER:

Ivor R. Elrifi, Reg. No. 39,529
Cynthia A. Kozakiewicz, Reg. No. 42,764
Attorneys for Applicants
MINTZ LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

Express Mail Label No.: EV 538966998 US
Date of Deposit: October 1, 2007

OCT 01 2007
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Shailubhai, *et al.*		
PATENT NUMBER:	7,041,786	ISSUE DATE:	May 9, 2006
SERIAL NUMBER:	10/107,814	EXAMINER:	Stephen L. Rawlings
FILING DATE:	March 28, 2002	ART UNIT:	1643
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Boston, Massachusetts
October 1, 2007

Mail Stop PETITIONS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT IN SUPPORT OF REQUEST UNDER 37 C.F.R. § 3.81

Pursuant to 37 C.F.R. § 3.81, Applicants hereby request that a Certificate of Correction to correct the assignee name be issued.

The instant application was filed on March 28, 2002, and was assigned to Synergy Pharmaceuticals Inc. in an Assignment recorded at Reel 013156 and Frame 0592 on August 1, 2002. A copy of the Notice of Recordation of Assignment Document from the instant application is attached to this statement as Exhibit A, and the executed Assignment Document to Synergy Pharmaceuticals Inc. is attached as Exhibit B.

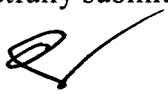
Applicants erroneously listed Callisto Pharmaceuticals in the PTOL-85B as the assignee of the invention, and this information was printed on the face of the above-referenced patent, which issued on May 9, 2006. Applicants have only recently become aware of this error.

Applicants hereby state that the failure to include the correct assignee name (Synergy Pharmaceuticals Inc.) on the PTOL-85B was inadvertent and the assignment with the correct assignee was submitted for recordation as set forth in 37 C.F.R. § 3.11 before the issuance of the above-reference patent. Also submitted herewith is the processing fee under 37 C.F.R. § 1.17(i), a Request for a Certificate of Correction, a Certificate of Correction and the appropriate fee under 37 C.F.R. § 1.20(a).

10/04/2007 EAYALEW1 00000028 7041786
01 FC:1464 130.00 OP

The Commissioner is invited to contact the undersigned by collect telephone call if there are any questions concerning this statement or the accompanying petition.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529
Cynthia A. Kozakiewicz, Reg. No. 42,764
Attorneys for Applicants
Tel: (617) 542-6000
Fax: (617) 542-2241

Customer Number 30623

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PATENT & TRADEMARK OFFICE

UNITED STATES PATENT AND TRADEMARK OFFICE

90128

OCTOBER 08, 2002

PTAS

PILLSBURY WINTHROP, LLP
RICHARD A. STEINBERG
P.O. BOX 10500
MCLEAN, VA 22102

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

102184451A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/01/2002

REEL/FRAME: 013156/0592
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SHAILUBHAI, KUNWAR

DOC DATE: 06/18/2002

ASSIGNOR:
JACOB, GARY S.

DOC DATE: 06/19/2002

ASSIGNEE:
SYNERGY PHARMACEUTICALS INC.
TWO EXCUTIVE DRIVE, SUITE 450
SOMERSET, NEW JERSEY 08873

SERIAL NUMBER: 10107814
PATENT NUMBER:

FILING DATE: 03/28/2002
ISSUE DATE:

JEEVON JONES, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

RECEIVED
OCT 15 2002
By

BOX ASSIGNMENTS

08-09-2002

DO NOT USE FOR TRADEMARKS

102184451

TO THE ASSISTANT COMMISSIONER C
SIR: PLEASE RECORD THE ATTACHED ORIGINAL DOCUMENT(S) OR COPY THEREOF.

1. NAME OF CONVEYING PARTY(IES) (ASSIGNORS(S)):

1. Kunwar Shailubhai	2. Gregory Nikiforovich
3. Gary S. Jacob	4.
5.	6.
7.	8.

ADDITIONAL NAME(S) OF CONVEYING PARTY(IES) ATTACHED? ☐YES ☒NO

OIPE SC174 AUG 0 1 2002 PATENT & TRADEMARK OFFICE

MRD 8-1-02

2. PARTY(IES) (ASSIGNEE(S)) RECEIVING INTEREST:

NAME: Synergy Pharmaceuticals Inc.

ADDRESS: Two Executive Drive, Suite 450, Somerset, New Jersey 08873

ADDITIONAL NAME(S) & ADDRESS(ES) ATTACHED? ☐YES ☒NO

3. NATURE OF CONVEYANCE (DOCUMENT):
(Submit herewith only one document for recordation—multiple copies of same Assignment signed by different inventors is one document)

☒ASSIGNMENT OF ☒WHOLE ☐PART INTEREST
☒ORIGINAL ☐FACSIMILE/PHOTOCOPY
☐CHANGE OF NAME ☐VERIFIED TRANSLATION
☐SECURITY ☐MERGER ☐OTHER:

EXEC. DATE: June 18 and 19, 2002

EXECUTION DATE(S) ON THE DECLARATION IF FILED HEREWITH: (**NOTE**: IF DATES ON DECLARATION AND ASSIGNMENT DIFFER SEE ATTY!) June 18 and 19, 2002

4.5 APPL. NO.(S) OR PAT NO.(S). OTHERS ON ADDITIONAL SHEET(S) attached? ☐YES ☐NO

A. PAT. APP. NO.(S) series code/serial no	M#	1st INVENTOR if not in item 1	B. PATENT NO(S)	M#	1st INVENTOR if not in item 1
10/107,814	0284943	Shailubhai			

5. Name & Address of Party to Whom Correspondence Concerning Document Should be Mailed:

Pillsbury Winthrop LLP
Intellectual Property Group
P.O. Box 10500McLean, VA 22102

6. NUMBER INVOLVED:
APPLNS 1 + PATS 0 = TOTAL = 1

7. AMOUNT OF FEE DUE: (Code 581)
ABOVE TOTAL x $40 = $40

5.5ATTY DKT:

P 0284943

MATTER NO. | CLIENT REF.

8. **PLEASE CHARGE** TO OUR DEPOSIT ACCOUNT NUMBER: 03-3975

UNDER ORDER NO | 081361 | 0284943
dup. sheet not required | CLIENT NO. | MATTER NO.

9. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Richard A Steinberg
Signature

10. Total number of pages including this cover sheet, attachments and document (do not file dup. Cover sheet)	3

Attorney: Richard A. Steinberg
Reg. No. 26,588 Date: August 1, 2002
Atty/Sec: RAS/kmh TEL: (703) 905-2039 FAX: (703) 905-2500

FILE WITH PTO RETURN RECEIPT (PAT-103A)

08/09/2002 LMUELLER 00000035 033975 10107814
01 FC:581 40.00 CH

Please return signed/recorded to:
Pillsbury Winthrop LLP
Intellectual Property Group
1600 Tysons Boulevard
McLean, VA 22102

Atty. Dkt. PMS 284943 | M# | Client Ref.

ASSIGNMENT
of U.S. Origin Patent Application

WHEREAS, the undersigned, to wit:

1) Kunwar SHAILUBHAI 2) Gregory NIKIFOROVICH
3) Gary S. JACOB 4)
5) 6)
7) 8)

(hereinafter collectively ASSIGNOR), has/have made an invention known as Dkt.
and entitled Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

for which an application for Letters Patent of the United States
☐ was executed even date herewith and is about to be filed in the United States Patent and Trademark Office;
☒ was filed on March 28, 2002, Appln. No. 10/107,814;

AND WHEREAS Synergy Pharmaceuticals Inc.
(hereinafter ASSIGNEE), duly organized and existing under the laws of the State of DELAWARE
and having its principal office and place of business at Two Executive Drive, Suite 450, Somerset, NJ 08873
desires to acquire an interest therein;

NOW, THEREFORE, in consideration of Ten Dollars ($10.00) and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the said ASSIGNOR, does hereby sell, assign and transfer unto ASSIGNEE, its successors, assigns and legal representatives, the full and exclusive right, title and interest to the said invention in the United States and all foreign countries, as described in the aforesaid application, and to the said application and to all continuations, divisions, reissues and substitutes of said application, together with the right of priority under the International Convention for the Protection of Industrial Property, Inter-American Convention Relating to Patents, Designs and Industrial Models, and any other international agreements to which the United States of America adheres, and ASSIGNOR hereby authorizes and requests the Commissioner of Patents to issue said Letters Patent to ASSIGNEE, for its interest as ASSIGNEE, its successors, assigns and legal representatives.

PAT-114B 1/01

AND ASSIGNOR hereby agrees to execute any papers requested by ASSIGNEE, its successors, assigns and legal representatives, deemed essential to ASSIGNEE's full protection and title in and to the invention hereby transferred.

ASSIGNOR furthermore agrees upon request of said ASSIGNEE, and without further remuneration, to execute any and all papers desired by said ASSIGNEE for the filing and granting of foreign applications and the perfecting of title thereto in said ASSIGNEE.

NOTE: The undersigned hereby authorizes Pillsbury Winthrop LLP of the above address to insert hereon any further identification necessary or desirable for recordation of this document.

Executed on the date(s) below indicated.

	Signature	Date Signed	Witness
1)	Name: Kunwar SHAILUBHAI	6/18/02	Lisa Asperlach
2)	Name: Gregory NIKIFOROVICH	6/19/02	Linda M. Ketchem
3)	Name: Gary S. JACOB	6/18/02	Lisa Asperlach
4)	Name:		
5)	Name:		
6)	Name:		
7)	Name:		
8)	Name:		

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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NOV 28 2007

OFFICE OF PETITIONS

MAYER, BROWN, ROWE & MAW LLP
71 SOUTH WACKER
CHICAGO IL 60606

In re Patent No. 7041786 :
Issue Date: 05/09/2006 :
Application Number: 10/107814 : ON PETITION
Filing Date: 03/28/2002 :
Attorney Docket Number: P 0284943 :
:

This is a decision on the paper filed on October 1, 2007, which is treated as a request under 37 CFR 3.81(b)[1] to correct the assignee on the front page of the above-identified patent by way of a Certificate of Correction.

The petition is **granted**.

Telephone inquires concerning this matter may be directed to the undersigned at 571.272.3231. Any questions concerning the issuance of the Certificate of Correction should be directed to the Certificates of Correction Branch at 703.305.8309.

The address in the request is different than the correspondence address. A courtesy copy of this decision is being mailed to the address in the request. All future correspondence, however, will be mailed solely to the address of record.

The application is referred to the Certificate of Corrections Branch for issuance of the Certificate of Correction.

D Wood

Douglas I. Wood
Senior Petitions Attorney
Office of Petitions

Cc:

MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON MA 02111

[1] See Official Gazette of 22 June, 2004.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

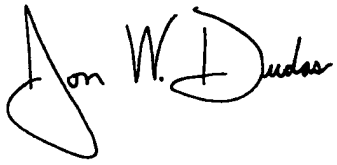
PATENT NO. : 7,041,786 B2
APPLICATION NO. : 10/107814
DATED : May 9, 2006
INVENTOR(S) : Shailubhai et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Title page item 73, the Assignee should be: "Synergy Pharmaceuticals Inc." (US).

Signed and Sealed this

Eighth Day of January, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Patent Number	7,041,786
Filing Date	Issued: May 9, 2006
First Named Inventor	Kunwar Shailubhai
Art Unit	1646
Examiner Name	Stephen L. Rawlings
Attorney Docket Number	40737-501001US

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Executed Power of Attorney and Statement under 37 CFR 3.73(b).

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO, P.C.		
Signature	/Cynthia Kozakiewicz/		
Printed name	Cynthia Kozakiewicz		
Date	February 23, 2010	Reg. No.	42,764

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	10/107,814
Filing Date	March 28, 2002
First Named Inventor	Kunwar Shailubhai
Title	GUANYLATE CYCLASE RECEPTOR AGONISTS FPR THE TREATMENT OF
Art Unit	1643
Examiner Name	Stephen L. Rawlings
Attorney Docket No.	40737-501001US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 30623

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number	Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country		Telephone		Email	

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	[signature]	Date	Feb. 18, 2010
Name	GARY S. JACOB	Telephone	212-297-0020
Title and Company	President & CEO, Synergy Pharmaceuticals Inc.		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Synergy Pharmaceuticals, Inc.

Application No./Patent No.: 7,041,786 Filed/Issue Date: May 9, 2006

Titled: GUANYLATE CYCLASE RECEPTOR AGONISTS FPR THE TREATMENT OF TISSUE INFLAMINATION AND CACINOGENESIS

Synergy Pharmaceuticals, Inc. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 021031, Frame 0438, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[X] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — Date: Feb. 18, 2010

GARY S. JACOB — Printed or Typed Name

President + CEO — Title

Electronic Acknowledgement Receipt

EFS ID:	7067654
Application Number:	10107814
International Application Number:	
Confirmation Number:	9117
Title of Invention:	GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS
First Named Inventor/Applicant Name:	Kunwar Shailubhai
Customer Number:	43569
Filer:	Cynthia A. Kozakiewicz/Victoria Hughes
Filer Authorized By:	Cynthia A. Kozakiewicz
Attorney Docket Number:	P 0284943
Receipt Date:	23-FEB-2010
Filing Date:	28-MAR-2002
Time Stamp:	14:42:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Trans.pdf	78298 67a775a7584c26d04ebc3d408bca92bf5fb69e7c	no	1

Warnings:	
Information:	

2	Power of Attorney	POA.pdf	43662 6f66db02c6a7c12ab2aca73e8b5deee79f2557ba	no	1
Warnings:					
Information:					
3	Assignee showing of ownership per 37 CFR 3.73(b).	Statement.pdf	40745 2ff8524110cf9b644581cda8c9f48890c897442b	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	162705	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943

CONFIRMATION NO. 9117

POWER OF ATTORNEY NOTICE

43569
MAYER BROWN LLP
P.O. Box. 2828
Chicago, IL 60690

OC000000040409200

Date Mailed: 03/04/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/03/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/dolipscomb/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943

CONFIRMATION NO. 9117

POA ACCEPTANCE LETTER

30623
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

OC000000040409208

Date Mailed: 03/04/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/03/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/dolipscomb/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☒ Practitioners associated with the Customer Number: **58249**

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☒ The address associated with Customer Number: **58249**

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

Synergy Pharmaceuticals Inc.
420 Lexington Avenue, Suite 2012
New York, NY 10170

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	Oct. 6, 2014
Name	Gary S. Jacob, Ph.D.	Telephone	
Title	President and Chief Executive Officer		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

American LegalNet, Inc.
www.FormsWorkflow.com

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Kunwar Shailubhai et al.

Application No./Patent No.: 10/107,814 Filed/Issue Date: 03/28/2002

Titled: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

Synergy Pharmaceuticals Inc., a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Kunwar Shailubhai et al. To: Synergy Pharmaceuticals Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 013156, Frame 0592, or for which a copy thereof is attached.

2. From: Kunwar Shailubhai et al. To: Synergy Pharmaceuticals Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 021031, Frame 0438, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[X] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — Date: Oct. 6 2014

Gary S. Jacob, Ph.D. — President and Chief Executive Officer
Printed or Typed Name — Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	20467443
Application Number:	10107814
International Application Number:	
Confirmation Number:	9117
Title of Invention:	GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS
First Named Inventor/Applicant Name:	Kunwar Shailubhai
Customer Number:	30623
Filer:	Cynthia A. Kozakiewicz/Donna Doyle
Filer Authorized By:	Cynthia A. Kozakiewicz
Attorney Docket Number:	40737-501001US
Receipt Date:	24-OCT-2014
Filing Date:	28-MAR-2002
Time Stamp:	16:53:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	SYPA_SB80_GeneralPOA.pdf	110734 e5cda96054c9fa05e6d856e71accc68030e266e6	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73.	SYPA_00101US_Statement.pdf	95069 51e7af6600dfb42a587f62afe9696ace8d5b5ef8	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	205803

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	40737-501001US

CONFIRMATION NO. 9117

POWER OF ATTORNEY NOTICE

30623
Mintz Levin/Boston Office
One Financial Center
Boston, MA 02111

OC000000071576766

Date Mailed: 10/29/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/rmturner myles/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	

CONFIRMATION NO. 9117

POA ACCEPTANCE LETTER

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000071576808

Date Mailed: 10/29/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/rmturner myles/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Date of Hand Delivery: February 7, 2017

Attorney Docket No. SYPA-001/01US 321994-2051 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	US Patent No.: 7,041,786 issued May 9, 2006
To:	Kunwar Shailubhai, Gregory Nikiforovich, and Gary Jacob
Assignee:	Synergy Pharmaceuticals, Inc.
Title:	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

RECEIVED
FEB 07 2017
PATENT EXTENSION
OPLA

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
U.S. Patent and Trademark Office
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicants, patent owners Synergy Pharmaceuticals, Inc. New York, NY request extension of the term of U.S. Patent Number 7,041,786 ("the '786 patent"), pursuant to 35 U.S.C. § 156. A copy of the '786 patent (with certificate of correction) is provided as Exhibit 1.

United States Patent No. 7,041,786 naming Kunwar Shailubhai, Gregory Nikiforovich, and Gary Jacob as inventors, entitled "Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis" issued on May 9, 2006. The entire right, title, and interest in the '786 patent was assigned to Synergy Pharmaceuticals, Inc. in Assignments recorded in the records of the United States Patent and Trademark Office at Reel/Frame 013156 / 0592 on August 1, 2002, and Reel/Frame 021031 / 0438 on May 30, 2008.[1] A copy of the Assignments is attached as Exhibit 2.

03/07/2017 SMOHAMM2 00000002 10107814
01 FC:1457 1120.00 DA

[1] The face of the patent incorrectly indicates that Callisto Pharmaceuticals is the assignee, however the Certificate of Correction corrects this to Synergy Pharmaceuticals, Inc.

Synergy Pharmaceuticals is the sponsor of New Drug Application ("NDA") No. 208745 for TRULANCE™ (also known as plecanatide or SP-304) which is claimed in U.S. Patent 7,041,786.

Applicants hereby request an extension of patent term under 37 C.F.R. § 1.730(c), by providing the following information required under convenience of the Office. The information is presented in a format that follows the paragraph numbering in 37 C.F.R. § 1.740.

A copy of the Power of Attorney is attached as Exhibit 3 confirming that the undersigned registered practitioner is authorized to act on behalf of Applicants.

(1) **Identification of the Approved Product [§ 1.740(a)(1)]**

The approved product, TRULANCE™, is a guanylate cyclase-C ("GCC) receptor agonist and contains an active ingredient, plecanatide. Plecanatide is a 16 amino acid peptide having the amino acid sequence shown below.

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu

(2) **Federal Statute Governing Regulatory Approval of the Approved Product [§ 1.740(a)(2)]**

The approved product, TRULANCE™, was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355).

(3) **Date of Approval for Commercial Marketing [§ 1.740(a)(3)]**

Synergy Pharmaceuticals, Inc. received permission for commercial marketing or use of TRULANCE™ under Section 505 of the Federal food, Drug, and Cosmetics Act (21 U.S.C. § 355) on January 19, 2017. A copy of the letter from the FDA approving marketing of TRULANCE™ (including a copy of the approved label) is attached as Exhibit 4.

(4) **Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§ 1.740(a)(4)]**

The active ingredient in TRULANCE™ is plecanatide, which has never been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act prior to the

approval of NDA 208745 by the Food and Drug Administration on January 19, 2017. TRULANCE™ was approved under 21 U.S.C.§ 355(b) for the treatment of chronic idiopathic constipation.

(5) **Statement Regarding Timeliness of Submission of Patent Term Extension Request [§ 1.740(a)(5)]**

This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The date of the last day on which the application could be submitted being March 20, 2017. The present application, therefore is timely submitted.

(6) **Complete Identification of the Patent for Which Extension is Being Sought [§ 1.740(a)(6)]**

The patent for which extension is being sought is identified as follows:

Inventors:	Kunwar Shailubhai Gregory Nikiforovich Gary Jacob
Patent No.:	US Patent No.: 7,041,786
Title:	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis
Issued:	May 9, 2006
Expires:	March 25, 2023 (including 362 days of PTA)

(7) **Copy of the Patent for Which and Extension is Being Sought [§ 1.740(a)(7)]**

A copy of US Patent No. 7,041,786, including entire specification and drawings (with certificate of correction) is attached as Exhibit 1.

(8) **Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§ 1.740(a)(8)]**

The most recent maintenance fee was timely paid. A copy of the most recent maintenance fee statement is attached as Exhibit 5.

No disclaimer or reexamination certificate has been filed and/or issued for US Patent No.: 7,041,786.

A certificate of correction for US Patent No.: 7,041,786 issued on January 8, 2008 (copy attached at Exhibit 1).

(9) **Statement on a New Page For Patent Claims on Approved Product [§ 1.740(a)(9)]**

The statements provided herein are made solely to comply with the requirements of 37 C.F.R § 1.740(a)(9). We note that, as the M.P.E.P. acknowledges, the requirement of 37 C.F.R § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed; and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicants as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale, or the importation of any product.

(a) At least the following claim of U.S. Patent No. 7,041,786 covers the approved product.

Specifically, the approved product is claimed in Claims 1, 2, 4 and 5.

(b) Pursuant to M.P.E.P. § 2573 and 37 C.F.R. § 1.740(a)(9), the following explanation is provided which shows how each of the above-listed claims of the patent claim the approved product, or a method of making or using the approved product.

Claims 1, 2, 4 and 5 of US Patent No. 7,041,786 are recited below, along with an explanation which shows how the claim reads on the approved product:

1. A peptide consisting of the amino acid sequence of SEQ ID NO:20.

The amino acid sequence of SEQ ID NO: 20 is Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu. This is the same amino acid sequence as plecanatide (see section 1 above), the active ingredient in TRULANCE™. Claim 1 accordingly reads on the approved product.

2. A composition in unit dose comprising a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO:20.

The amino acid sequence of SEQ ID NO: 20 is Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu. This is the same amino acid sequence as plecanatide (see section 1 above), the active ingredient in TRULANCE™. In addition, TRULANCE™ is approved in a unit dose of 3 mg tablets. Claim 2 accordingly reads on the approved product.

4. The composition of either claim 2 or 3, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution and an inhalation formulation.

Claim 4 depends from, *inter alia*, claim 2, which recites a composition in unit dose comprising a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO: 20. The amino acid sequence of SEQ ID NO: 20 is Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu. This is the same amino acid sequence as plecanatide, the active ingredient in TRULANCE™. In addition, TRULANCE™ is approved in a unit dose of 3 mg tablets. Claim 4 accordingly reads on the approved product.

5. The composition of either claim 2 or 3, further comprising one or more excipients.

Claim 5 depends from, *inter alia*, claim 2, which recites a composition in unit dose comprising a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO: 20. The amino acid sequence of SEQ ID NO: 20 is Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu. This is the same amino acid sequence as plecanatide, the active ingredient in TRULANCE™. In addition, TRULANCE™ is approved in a unit dose of 3 mg tablets. Moreover, TRULANCE™ contains magnesium stearate and microcrystalline cellulose as excipients. Claim 5 accordingly reads on the approved product.

(10) Provide On a New Page a Statement of Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period [§ 1.740(a)(10)]

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable review period are as follows:

(a) Patent Issue Date

US Patent No.: 7,041,786 issued on May 9, 2006. (Exhibit 1)

(b) IND Effective Date [35 U.S.C.§ 156(a)(1)(B)(i); 37 C.F.R. § 1.740(a)(10)(i)(A)]

Investigational New Drug Application (IND 74,883) was submitted on April 2, 2008 and the IND was effective on May 2, 2008. (See Exhibit 6)

(c) NDA Submission Date [35 U.S.C.§ 156(g)(1)(B)(i); 37 C.F.R. § 1.740(a)(10)(i)(B)]

New Drug Application (NDA 208745) was submitted on January 29, 2016. (Exhibit 4)

(d) NDA Issue Date [35 U.S.C.§ 156(g)(1)(B)(ii); 37 C.F.R. § 1.740(a)(10)(i)(C)]

New Drug Application (NDA 208745) was approved on January 19, 2017. (Exhibit 4)

(11) Provide On a New Page a Summary of Significant Events During Regulatory Review Period [§ 1.740(a)(11)]

Investigational New Drug Application (IND 74,883) for TRULANCE™ was submitted on April 2, 2008 and the IND was effective on May 2, 2008. New Drug Application (NDA 208745) for TRULANCE™ was submitted on January 29, 2016. New Drug Application (NDA 208745) was approved on January 19, 2017.

A brief description of the significant activities undertaken during the applicable regulatory review period with respect to the TRULANCE™ and the significant dates applicable to such activities is attached as Exhibit 6.

(12) Statement on a New Page Concerning Eligibility for and Duration of Extension Sought Under § 156 [§ 1.740(a)(12)]

(12)(A) Applicants are of the opinion that US Patent No. 7,041,786 is eligible for an extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such an extension as follows:

(a) 35 U.S.C. § 156(a): US Patent No. 7,041,786 claims a product.

(b) 35 U.S.C. § 156(a)(1): The term of US Patent No. 7,041,786 expires March 25, 2023, and thus has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2): The term of US Patent No. 7,041,786 has never been extended under this provision of the law.

(d) 35 U.S.C. § 156(a)(3): The application is submitted by Cooley, LLP, an agent of the patent owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and the rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4): The product TRULANCE™ has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A): The commercial marketing or use of TRULANCE™ after the regulatory review period is the first permitted commercial marketing or use of product under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4): No other patent has been extended for the same regulatory review period for the product TRULANCE™.

12(B) The length of extension of the patent term of US Patent No. 7,041,786 claimed by Applicants is 1771 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on May 2, 2008 and ended on January 19, 2017 which is a total of 3185 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on May 2, 2008 and ended on January 28, 2016 which is 2828 days; and

(ii) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on January 29, 2016 and ended on January 19, 2017 which is 357 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(B)(a) above (3185 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which US Patent No. 7,041,786 issued is 0 days, and,

(ii) The number of days during which Applicants did not act with due diligence, which is 0 days, and

(iii) One-half of (2828 days), which is 1414 days;

(iv) The regulatory review period is calculated by subtracting the number of days determined in subparagraph 12(B)(b)(i)-(iii) from the entire regulatory review period, as determined in subparagraph 12(B)(a) (which is 3185 minus 1414 days from (iii)), which equals 1771 days;

(c) The number of days as determined in sub-paragraph 12(B)(b)(iv) (1771 days) when added to the term of the patent (March 25, 2023) would result in the date January 29, 2028;

(d) Fourteen years, when added to the date of NDA approval (January 19, 2017) would result in the date January 19, 2031.

(e) The earlier date as determined in subparagraphs 12(B)(c) and 12(B)(d) is January 29, 2028.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five years. Five years when added to the expiration date of the patent (March 25, 2023) would result in the date March 25, 2028.

(g) The earlier date as determined in subparagraph 12(B)(e) and 12(B)(f) is January 29, 2028 which is 1771 days from the expiration date of the patent.

(13) Statement Pursuant to 37 C.F.R. [§ 1.740(a)(13)]

Applicants acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. § 1.765.

(14) Applicable Fee [§ 1.740(a)(14)]

The prescribed fee for receiving and acting upon this application is to be charged to Deposit Account 50-1283 as authorized in the attached letter, which is submitted in triplicate.

(15) Name and Address for correspondence [§ 1.740(a)(15)]

Correspondence related to this application for extension of the patent term of US Patent No. 7,041,786 should be addressed to:

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Date of Hand Delivery: February 7, 2017

(16) Additional Copies of the Application for Extension [§ 1.740(a)(16)]

This application for extension of the patent term of US Patent No. 7,041,786 is being submitted as ONE original and TWO additional copies thereof. Applicants hereby certify that the copies submitted herein are true copies.

Transmitted herewith IN THREE COPIES total is the application for extension of patent term of US Patent No. 7,041,786 under 35 U.S.C. § 156. Please charge $1,120.00 in accordance with 37 C.F.R. § 1.20/(j)(1) to Cooley LLP, Deposit Account 50-1283. The undersigned has authority to request that the Office charge this account for this application.

Respectfully submitted,

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Date of Hand Delivery: February 7, 2017

Index of Attachments:

Exhibit 1: Copy of US Patent No. 7,041,786, with Certificate of Correction

Exhibit 2: Copy of the Assignment from Inventors to Synergy Pharmaceuticals, Inc.

Exhibit 3: Authorization of Agent/Power of Attorney for US Patent No. 7,041,786

Exhibit 4: Copy of letter from the FDA approving marketing of TRULANCE™ Including Copy of the Approved label for TRULANCE™

Exhibit 5: Maintenance Fee Statement for US Patent No. 7,041,786

Exhibit 6: Brief Description of Significant Activities During Applicable Regulatory Review

US007041786B2

(12) **United States Patent**
Shailubhai et al.

(10) **Patent No.: US 7,041,786 B2**
(45) **Date of Patent: May 9, 2006**

(54) **GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS**

(75) Inventors: **Kunwar Shailubhai**, Blue Bell, PA (US); **Gregory Nikiforovich**, St. Louis, MO (US); **Gary S. Jacob**, Creve Coeur, MO (US)

(73) Assignee: **Callisto Pharmaceuticals**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 362 days.

(21) Appl. No.: **10/107,814**

(22) Filed: **Mar. 28, 2002**

(65) **Prior Publication Data**

US 2003/0073628 A1 Apr. 17, 2003

Related U.S. Application Data

(60) Provisional application No. 60/348,646, filed on Jan. 17, 2002.

(51) **Int. Cl.**
A61K 38/12 (2006.01)

(52) **U.S. Cl.** **530/317**; 530/300; 530/326; 514/10; 514/13

(58) **Field of Classification Search** 530/317, 530/300, 326; 514/10, 13
See application file for complete search history.

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(57) **ABSTRACT**

A method of treatment of inflamed, pre-cancerous or cancerous tissue or polyps in a mammalian subject is disclosed. The treatment involves administration of a composition of at least one peptide agonist of a guanylate cyclase receptor and/or other small molecules that enhance intracellular production of cGMP. The at least one peptide agonist of a guanylate cyclase receptor may be administered either alone or in combination with an inhibitor of cGMP-dependent phosphodiesterase. The inhibitor may be a small molecule, peptide, protein or other compound that inhibits the degradation of cGMP. Without requiring a particular mechanism of action, this treatment may restore a healthy balance between proliferation and apoptosis in the subject's population of epithelial cells, and also suppress carcinogenesis. Thus, the method may be used to treat, inter alia, inflammation, including gastrointestinal inflammatory disorders, general organ inflammation and asthma, and carcinogenesis of the lung, gastrointestinal tract, bladder, testis, prostate and pancreas, or polyps.

6 Claims, No Drawings

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GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. provisional application No. 60/348,646, filed on Jan. 17, 2002.

FIELD OF THE INVENTION

The present invention relates to the therapeutic use of guanylate cyclase receptor agonists as a means for enhancing the intracellular production of cGMP. The agonists may be used either alone or in combination with inhibitors of cGMP-specific phosphodiesterase to prevent or treat cancerous, pre-cancerous and metastatic growths, particularly in the gastrointestinal tract and lungs. In addition, the agonists may be used in the treatment of inflammatory disorders such as ulcerative colitis and asthma.

BACKGROUND OF THE INVENTION

Uroguanylin, guanylin and bacterial ST peptides are structurally related peptides that bind to a guanylate cyclase receptor and stimulate intracellular production of cyclic guanosine monophosphate (cGMP) (1–6). This results in the activation of the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane channel for efflux of chloride from enterocytes lining the intestinal tract (1–6). Activation of CFTR and the subsequent enhancement of transepithelial secretion of chloride leads to stimulation of sodium and water secretion into the intestinal lumen. Therefore, by serving as paracrine regulators of CFTR activity, cGMP receptor agonists regulate fluid and electrolyte transport in the GI tract (1–6; U.S. Pat. No. 5,489,670).

The process of epithelial renewal involves the proliferation, migration, differentiation, senescence, and eventual loss of GI cells in the lumen (7,8). The GI mucosa can be divided into three distinct zones based on the proliferation index of epithelial cells. One of these zones, the proliferative zone, consists of undifferentiated stem cells responsible for providing a constant source of new cells. The stem cells migrate upward toward the lumen to which they are extruded. As they migrate, the cells lose their capacity to divide and become differentiated for carrying out specialized functions of the GI mucosa (9). Renewal of GI mucosa is very rapid with complete turnover occurring within a 24–48 hour period (9). During this process mutated and unwanted cells are replenished with new cells. Hence, homeostasis of the GI mucosa is regulated by continual maintenance of the balance between proliferation and apoptotic rates (8).

The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a wide variety of different circumstances, e.g., in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone (10). The proliferation index has been observed to be much higher in pathological cases of ulcerative colitis and other GI disorders (11). Thus, intestinal hyperplasia is the major promoter of gastrointestinal inflammation and carcinogenesis.

In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of GI mucosa. Previously published data in WO 01/25266 suggests a peptide with the active domain of uroguanylin may function as an inhibitor of polyp development in the colon and may constitute a treatment of colon cancer. However, the mechanism by which this is claimed to occur is questionable in that WO 01/25266 teaches uroguanylin agonist peptides that bind specifically to a guanylate cyclase receptor, termed GC-C, that was first described as the receptor for *E. coli* heat-stable enterotoxin (ST) (4). Knockout mice lacking this guanylate cyclase receptor show resistance to ST in intestine, but effects of uroguanylin and ST are not disturbed in the kidney in vivo (3). These results were further supported by the fact that membrane depolarization induced by guanylin was blocked by genistein, a tyrosine kinase inhibitor, whereas hyperpolarization induced by uroguanylin was not effected (12,13). Taken together these data suggest that uroguanylin also binds to a currently unknown receptor, which is distinct from GC-C.

Other papers have reported that production of uroguanylin and guanylin is dramatically decreased in pre-cancerous colon polyps and tumor tissues (14–17). In addition, genes for both uroguanylin and guanylin have been shown to be localized to regions of the genome frequently associated with loss of heterozygosity in human colon carcinoma (18–20). Taken together, these findings indicate that uroguanylin, guanylin and other peptides with similar activity may be used in the prevention or treatment of abnormal colon growths. This proposal is bolstered by a recent study demonstrating oral administration of uroguanylin inhibits polyp formation in mice (15,16).

Uroguanylin and guanylin peptides also appear to promote apoptosis by controlling cellular ion flux. Alterations in apoptosis have been associated with tumor progression to the metastatic phenotype. While a primary gastrointestinal (GI) cancer is limited to the small intestine, colon, and rectum, it may metastasize and spread to such localities as bone, lymph nodes, liver, lung, peritoneum, ovaries, brain. By enhancing the efflux of K^+ and influx of Ca^{++}, uroguanylin and related peptides may promote the death of transformed cells and thereby inhibit metastasis.

One of the clinical manifestations of reduced CFTR activity is the inflammation of airway passages (21). This effect may be due to CTFR regulating the expression of NF-KB, chemokines and cytokines (22–25). Recent reports have also suggested that the CFTR channel is involved in the transport and maintenance of reduced glutathione, an antioxidant that plays an important role in protecting against inflammation caused by oxidative stress (39). Enhancement of intracellular levels of cGMP by way of guanylate cyclase activation or by way of inhibition of cGMP-specific phosphodiesterase would be expected to down-regulate these inflammatory stimuli. Thus, uroguanylin-type agonists should be useful in the prevention and treatment of inflammatory diseases of the lung (e.g., asthma), bowel (e.g., ulcerative colitis and Crohn's disease), pancreas and other organs.

Overall, it may be concluded that agonists of guanylate cyclase receptor such as uroguanylin have potential therapeutic value in the treatment of a wide variety of inflammatory conditions, cancer (particularly colon cancer) and as anti-metastatic agents. The development of new agonists is therefore of substantial clinical importance.

SUMMARY OF THE INVENTION

The present invention is based upon the development of new agonists of guanylate cyclase receptor, and new uses of naturally occurring agonists. The agonists are analogs of uroguanylin, many of which have superior properties either in terms of improved receptor activation, stability, activity at low pH or reduced adverse effects. The peptides may be used to treat any condition that responds to enhanced intracellular levels of cGMP. Intracellular levels of cGMP can be increased by enhancing intracellular production of cGMP and/or by inhibition of its degradation by cGMP-specific phosphodiesterases. Among the specific conditions that can be treated or prevented are inflammatory conditions, cancer, polyps, and metastasis.

In its first aspect, the present invention is directed to a peptide consisting essentially of the amino acid sequence of any one of SEQ ID NOs:2–21 and to therapeutic compositions which contain these peptides. The term "consisting essentially of" includes peptides that are identical to a recited sequence identification number and other sequences that do not differ substantially in terms of either structure or function. For the purpose of the present application, a peptide differs substantially if its structure varies by more than three amino acids from a peptide of SEQ ID NOs:2–21 or if its activation of cellular cGMP production is reduced or enhanced by more than 50%. Preferably, substantially similar peptides should differ by no more than two amino acids and not differ by more than about 25% with respect to activating cGMP production. The most preferred peptide is a bicycle having the sequence of SEQ ID NO:20.

The peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The term "unit dose form" refers to a single drug delivery entity, e.g., a tablet, capsule, solution or inhalation formulation. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient (typically, between 100 μg and 3 g). What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art. For example, it may constitute a reduction in inflammation, a shrinkage of polyps or tumors, a reduction in metastatic lesions, etc.

The invention also encompasses combination therapy utilizing a guanylate cyclase receptor agonist administered either alone or together with an inhibitor of cGMP-dependent phosphodiesterase, an anti-inflammatory agent or an anticancer agent. These agents should be present in amounts known in the art to be therapeutically effective when administered to a patient. Anti-neoplastic agents may include alkylating agents, epipodophyllotoxins, nitrosoureas, antimetabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular anti-neoplastic agents may include tamoxifen, TAXOL™, etoposide and 5-fluorouracil. Antiviral and monoclonal antibody therapies may be combined with chemotherapeutic compositions comprising at least one guanylate cyclase receptor agonist in devising a treatment regimen tailored to a patient's specific needs.

In another aspect, the invention is directed to a method for preventing, treating or retarding the onset of cancer, particularly cancer of epithelial cells, or polyps in a subject by administering a composition comprising an effective amount of a guanylate cyclase receptor agonist, preferably a synthetic guanylate cyclase receptor agonist. The term "effective amount" refers to sufficient agonist to measurably increase intracellular levels of cGMP. The term "synthetic" refers to a peptide created to bind a guanylate cyclase receptor, but containing certain amino acid sequence substitutions not present in known endogenous guanylate cyclase agonists, such as uroguanylin. The agonist should be a peptide selected from those defined by SEQ ID NOs:2–21 and which are listed in Tables 2 and 3. Also included in the invention are methods of treating primary cancers, other than primary colon cancer, by administering an effective dosage of a peptide selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide. Any known form of uroguanylin or guanylin can be used for this purpose, although the human peptides are preferred.

The invention also includes methods of preventing or treating tumor metastasis from a primary tumor mass. Metastatic tumor cells having guanylate cyclase receptors may be targeted by peptides generated according to the invention. In a preferred embodiment, the targeted receptor is found on cells of gastrointestinal (GI) cancers and on metastasized cells derived from those cancers. Such receptors are typically transmembrane proteins with an extracellular ligand-binding domain, a membrane-spanning domain, and an intracellular domain with guanylate cyclase activity. Although the invention is not bound by any particular mechanism of action, it is believed that the peptides will act by binding to these cellular receptors and inducing apoptosis. Metastatic tumors may also be treated by administering any known form of uroguanylin or guanylin (preferably human) or by administering *E. coli* ST peptide.

Peptides may be administered either alone or together with one or more inhibitors of cGMP dependent phosphodiesterase. Examples of cGMP dependent phosphodiesterase inhibitors include suldinac sulfone, zaprinast, and motapizone. Treatable forms of cancer include breast cancer, colorectal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, and testicular cancer. Colon carcinogenesis may be prevented by inhibiting precancerous colorectal polyp development via administration of a composition according to the invention. It is believed that the peptides should be especially effective with respect to the treatment of colon cancer and in preventing the metastasis of colon tumors.

In another aspect, the invention is directed to a method for treating, preventing, or retarding the onset of organ inflammation (e.g., inflammation associated with the GI tract, asthma, nephritis, hepatitis, pancreatitis, bronchitis, or cystic fibrosis) of a subject by administering a composition comprising an agonist of a guanylate cyclase receptor that enhances intracellular production of cGMP. Preferred peptide agonists are selected from the group defined by SEQ ID NOs:2–21 shown in Tables 2 and 3, or uroguanylin, or guanylin, or *E.coli* ST peptide. These peptides may optionally be administered with one or more inhibitors of cGMP dependent phosphodiesterase, e.g., suldinac sulfone, zaprinast, or motapizone. In a preferred embodiment, the invention is directed to a method of treating an inflammatory disorder in a mammalian gastrointestinal tract. The inflammatory disorder may be classified as an inflammatory bowel disease, and more particularly may be Crohn's disease or ulcerative colitis. Administration may be enteric, and employ formulations tailored to target enterocytes.

In a broader sense, the invention includes methods of inducing apoptosis in a patient by administering an effective amount of a peptide having the sequence of any one of SEQ ID NO:2–SEQ ID NO:21, or uroguanylin, or guanylin or *E. coli* ST peptide. An "effective amount" of peptide, in this sense, refers to an amount sufficient to increase apoptosis in

a target tissue. For example, sufficient peptide may be given to induce an increased rate of cell death in a neoplastic growth.

The most preferred peptide for use in the methods described above is the peptide defined by SEQ ID NO:20. The sequence is as follows (see also Table 3):

Asn[1] Asp[2] Glu[3] Cys[4] Glu[5] Leu[6] Cys[7] Val[8] Asn[9] Val[10] Ala[11] Cys[12] Thr[13] Gly[14] Cys[15] Leu[16]
* ** * **

and wherein there is one disulfide linkage between the cysteine at position 4 and the cysteine at position 12; and a second disulfide linkage between the cysteine at position 7 and the cysteine at position 15 (SEQ ID NO:20). This peptide has been found to have enhanced biological activity as an agonist of cGMP production due to its enhanced binding constant for the guanylate cyclase receptor, and is superior to uroguanylin with regard to temperature and protease stability and with regard to its biological activity at the physiologically favorable pH range (pH 6 to 7) in the large intestine.

The guanylate cyclase receptor agonists used in the methods described above may be administered either orally, systemically or locally. Dosage forms include preparations for inhalation or injection, solutions, suspensions, emulsions, tablets, capsules, topical salves and lotions, transdermal compositions, other known peptide formulations and pegylated peptide analogs. An effective dosage of the composition will typically be between about 1 μg and about 10 mg per kilogram body weight, preferably between about 10 μg to 5 mg of the compound per kilogram body weight. Adjustments in dosage will be made using methods that are routine in the art and will be based upon the particular composition being used and clinical considerations. Agonists may be administered as either the sole active agent or in combination with other drugs, e.g., an inhibitor of cGMP-dependent phosphodiesterase. In all cases, additional drugs should be administered at a dosage that is therapeutically effective using the existing art as a guide. Drugs may be administered in a single composition or sequentially.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based upon several concepts. The first is that there is a cGMP-dependent mechanism which regulates the balance between cellular proliferation and apoptosis and that a reduction in cGMP levels, due to a deficiency of uroguanylin/guanylin and/or due to the activation of cGMP-specific phosphodiesterases, is an early and critical step in neoplastic transformation. A second concept is that the release of arachidonic acid from membrane phospholipids, which leads to the activation of $cPLA_2$, COX-2 and possibly 5-lipoxygenase during the process of inflammation, is down-regulated by a cGMP-dependent mechanism, leading to reduced levels of prostaglandins and leukotrienes, and that increasing intracellular levels of cGMP may therefore produce an anti-inflammatory response. In addition, a cGMP-dependent mechanism, is thought to be involved in the control of proinflammatory processes. Therefore, elevating intracellular levels of cGMP may be used as a means of treating and controlling inflammatory bowel diseases such as ulcerative colitis and Crohn's disease and other organ inflammation (e.g., associated with asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis).

Without intending to be bound by any theory, it is envisioned that ion transport across the plasma membrane may prove to be an important regulator of the balance between cell proliferation and apoptosis that will be affected by compositions altering cGMP concentrations. Uroguanylin has been shown to stimulate K^+ efflux, Ca^{++} influx and water transport in the gastrointestinal tract (3). Moreover, atrial natriuretic peptide (ANP), a peptide that also binds to a specific guanylate cyclase receptor, has also been shown to induce apoptosis in rat mesangial cells, and to induce apoptosis in cardiac myocytes by a cGMP mechanism (26–29). It is believed that binding of the present agonists to a guanylate cyclase receptor stimulates production of cGMP. This ligand-receptor interaction, via activation of a cascade of cGMP-dependent protein kinases and CFTR, is then expected to induce apoptosis in target cells. Therefore, administration of the novel peptides defined by SEQ ID NOs:2–21, as shown in Tables 2 and 3, or uroguanylin, or guanylin or *E. coli* ST peptide is expected to eliminate or, at least retard, the onset of inflammatory diseases of the GI tract and general organ inflammation (e.g., asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis).

In another aspect, the invention is directed to a method for preventing, treating or retarding the onset of cancer, particularly cancer of epithelial cells, in a subject by administering a composition comprising an effective amount of a guanylate cyclase receptor agonist, preferably a synthetic a guanylate cyclase receptor agonist. The term "effective amount" refers to sufficient agonist to measurably increase intracellular levels of cGMP. The term "synthetic" refers to a peptide created to bind a guanylate cyclase receptor, but containing certain amino acid sequence substitutions not present in known endogenous guanylate cyclase agonists, such as uroguanylin. The agonist should be a peptide selected from those defined by SEQ ID NOs:2–21 and which are listed in Tables 2 and 3. Also included in the invention are methods of treating primary and metastatic cancers, other than primary colon cancer, by administering an effective dosage of a peptide selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide. Any known form of uroguanylin or guanylin can be used for this purpose, although the human peptides are preferred.

The cGMP-dependent mechanism that regulates the balance between cellular proliferation and apoptosis in metastatic tumor cells may serve as a mechanism for targeting and treating metastatic tumors. The liver is the most common site of metastasis from a primary colorectal cancer. Toward later stages of disease, colorectal metastatic cells may also invade other parts of the body. It is important to note that metastatic cells originating from the primary site in the gastrointestinal tract typically continue to express guanylate cyclase receptors and therefore, these cells should be sensitive to apoptosis therapy mediated by intestinal guanylate cyclase receptors. Peptides having uroguanylin activity, when used either alone or in combination with specific inhibitors of cGMP-phosphodiesterase, also retard the onset

of carcinogenesis in gut epithelium by restoring a healthy balance between cell proliferation and apoptosis via a cGMP-mediated mechanism.

As used herein, the term "guanylate cyclase receptor" refers to the class of guanylate cyclase receptors on any cell type to which the inventive agonist peptides or natural agonists described herein bind.

As used herein, the term "guanylate cyclase receptor-agonist" refers to peptides and/or other compounds that bind to a guanylate cyclase receptor and stimulate cGMP production. The term also includes all peptides that have amino acid sequences substantially equivalent to at least a portion of the binding domain comprising amino acid residues 3–15 of SEQ ID NO:1. This term also covers fragments and pro-peptides that bind to guanylate cyclase receptor and stimulate cGMP production. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to a guanylate cyclase receptor and stimulate cGMP production.

Strategy and Design of Novel Guanylate Cyclase Receptor Agonists

Uroguanylin is a peptide secreted by the goblet and other epithelial cells lining the gastrointestinal mucosa as pro-uroguanylin, a functionally inactive form. The human pro-peptide is subsequently converted to the functionally active 16 amino acid peptide set forth in SEQ ID NO:1 (human uroguanylin sequence, see Table 2) in the lumen of the intestine by endogenous proteases. Since uroguanylin is a heat-resistant, acid-resistant, and proteolysis-resistant peptide, oral or systemic administration of this peptide and/or other peptides similar to the functionally active 16 amino acid peptide sequence of SEQ ID NO:1 may be effectively employed in treatment methods.

Peptides similar to, but distinct from, uroguanylin are described below, including some which produce superior cGMP enhancing properties and/or other beneficial characteristics (e.g., improved temperature stability, enhanced protease stability, or superior activity at preferred pH's) compared to previously known uroguanylin peptides. The peptides may be used to inhibit GI inflammation and for treating or preventing the onset of polyp formation associated with gut inflammation. Epithelial tissues susceptible to cancer cell formation may also be treated. The guanylate cyclase receptor agonists described have the amino acid sequences shown in Tables 2 and 3. The "binding domain" for agonist-receptor interaction includes the amino acid residues from 3–15 of SEQ ID NO:1.

Molecular modeling was applied to the design of novel guanylate cyclase receptor agonists using methods detailed in (30). It consisted of energy calculations for three compounds known to interact with guanylate cyclase receptors, namely for human uroguanylin, bicyclo [4.12: 7,15]Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16} (UG, SEQ ID NO:1); human guanylin, bicyclo [4.12: 7.15]Pro^{1}-Gly^{2}-Thr^{3}-Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Tyr^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15} (GU, SEQ ID NO:22); and *E. coli* small heat-stable enterotoxin, tricyclo [6.10; 7.15; 11–18] Asn^{1}-Ser^{2}-Ser^{3}-Asn^{4}-Tyr^{5}-Cys^{6}-Cys^{7}-Glu^{8}-Leu^{9}-Cys^{10}-Cys^{11}-Asn^{12}-Pro^{13}-Ala^{14}-Cys^{15}-Thr^{16} -Gly^{17}-Cys^{18}-Tyr^{19} (ST, SEQ ID NO:23). Geometrical comparisons of all possible low-energy conformations for these three compounds were used to reveal the common 3D structures that served as the "templates" for the bioactive conformation, i.e., for the conformation presumably adopted by GU, UG and ST during interaction with receptor. It allowed designing novel analogs with significantly increased conformational population of the bioactive conformation at the expense of other low-energy conformations by selecting individual substitutions for various amino acid residues.

Energy calculations were performed by use of build-up procedures (30). The ECEPP/2 potential field (31,32) was used assuming rigid valence geometry with planar trans-peptide bonds, including that for Pro^{13} in ST. The ω angle in Pro^{13} was allowed to vary. Aliphatic and aromatic hydrogens were generally included in united atomic centers of CH_n type; H^{α}-atoms and amide hydrogens were described explicitly.

The main calculation scheme involved several successive steps. First, the sequences of the two monocyclic model fragments (three fragments for ST), Ac-cyclo (Cys^{i}- . . . -Cys^{j})-NMe, were considered, where all residues except Cys, Gly and Pro were replaced by alanines; the i and j values corresponded to the sequences of GU, UG and ST. At this step, all possible combinations of local minima for the peptide backbone for each amino acid residue were considered, i.e., the minima in the Ramachandran map of E, F, C, D, A and A* types (according to the notation in (33)) for the Ala residue; of E*, F*, C*, D*, A, E, F, C D and A* types for the Gly residue; and of F, C and A types for Pro. For each backbone conformation, one optimal possibility to close a cycle employing the parabolic potential functions, intrinsic to the ECEPP force field, was found by checking an energy profile of rotation around the dihedral angle χ_1 for the D-Cys residue.

Totally, as many as ca. 180,000 conformations for each of the cyclic moieties were considered. Then, the conformers satisfying the $E-E_{min}<\Delta E=15$ kcal/mol criterion and differing by more than 40° in at least one value of any backbone dihedral angle were selected (from ca. 3,000 to 8,000 conformations for different model fragments). At the next step, the selected conformations of the matching monocyclic fragments were overlapped to create possible conformations of the bicyclic model fragments (the tricyclic fragments in the case of ST). Typically, this procedure yielded ca. 20,000–30,000 conformations. All these conformations were submitted for a new cycle of energy calculations, which resulted in 191 conformations satisfying the $E-E_{min}<\Delta E=20$ kcal/mol criterion for the ST model fragment and in 6,965 conformations satisfying the same criterion for the GU/UG model fragment. After that, the missing side chains in the model fragments were restored, and energy calculations were performed again, the dihedral angle values of side chain groups (except the χ_1 angle for the Cys residues) and of the terminal groups of the backbone being optimized before energy minimization to achieve their most favorable spatial arrangements, employing an algorithm previously described (34). For the UG 4–15 fragment, 632 conformations satisfied the criterion of ΔE=20 kcal/mol; 164 of them satisfied the more stringent criterion of ΔE=12 kcal/mol, which corresponds to the accepted criterion of 1 kcal/mol/residue (30). Subsequent elongation of the UG 4–15 fragment to 3–16, and then to the entire UG molecule was performed by the same build-up procedure. Finally, 31 backbone conformations of UG were found as satisfying the criterion of ΔE=16 kcal/mol.

Geometrical comparison of conformers was performed in the following manner. The best fit in the superposition for the atomic centers in a pair of conformers was assessed to check the level of geometrical similarity between the two conformers, according to (35). The criterion for geometrical similarity was the rms value, which was calculated for a pair of conformations A and B as follows:

$$rms=(1/N)\Sigma^{N}_{i=1}[(x^{A}_{i}-x^{B}_{i})^2+(y^{A}_{i}-y^{B}_{i})^2+(z^{A}_{i}-z^{B}_{i})^2]^{1/2},$$

where N is the number of the C^{α}-atom pairs chosen for superposition, and x, y and z are the Cartesian coordinates. By the criterion of geometrical similarity of rms<2.0 Å, low-energy conformations of the rigid conformational fragment UG 4–15 fell into seven conformational families. One of them consists of the same six conformers that are similar both to 1UYA and 1ETN; this family contains also the lowest-energy conformer of UG. (1UYA and 1ETN are the experimentally defined 3D structures of UG and ST, respectively, which are known to possess high biological activity (36,37); the 3D structures were available in the Protein Data Bank.)

TABLE 1

The values of dihedral angles (in degrees) for peptide backbone in the "template" conformation of UG

		Conformer's #					
Residue	Angle	1	3	9	22	25	27
Cys^{4}	ψ	−37	−41	−40	−55	−38	−54
Glu^{5}	φ	−71	−67	−72	−69	−68	−70
	ψ	−50	−47	−48	−33	−43	−22
Leu^{6}	φ	−86	−86	−85	−81	−88	−91
	ψ	163	165	160	153	160	156
Cys^{7}	φ	−79	−82	−79	−83	−79	−81
	ψ	74	68	78	67	75	72
Val^{8}	φ	−120	−114	−126	−124	−125	−128
	ψ	−65	−57	−62	−55	−60	−64
Asn^{9}	φ	−83	−95	−82	−88	−89	−82
	ψ	119	113	134	118	111	116
Val^{10}	φ	−84	−82	−97	−90	−82	−82
	ψ	−21	−13	−16	−4	−15	−16
Ala^{11}	φ	−79	−86	−87	−89	−85	−80
	ψ	−32	−21	−35	−35	−18	−27
Cys^{12}	φ	−86	−92	−78	−79	−95	−90
	ψ	−52	−53	−55	−57	−53	−54
Thr^{13}	φ	−129	−121	−127	−119	−118	−130
	ψ	111	153	141	155	141	119
Gly^{14}	φ	−64	−78	−78	−80	−78	−68
	ψ	83	64	68	62	67	78
Cys^{15}	φ	−139	−160	−150	−156	−78	−131

The dihedral angles φ and ψ, values that determine the overall 3D shape of this UG fragment, are similar (Table 1). It allowed performing preliminary design of new analogs aimed at stabilizing this particular family of conformations employing the known local conformational limitations imposed by various types of amino acids.

For instance, it is known that Gly is more conformationally flexible compared to any other L-amino acid residue, since Gly may adopt conformations with any of the four combinations of signs for φ and ψ, i.e., −,+; −,−; +,+; and +,−. The last combination is sterically forbidden for the L-amino acids, as Ala. Therefore, substitution of Gly^{14} for Ala^{14} should limit conformational flexibility in position 14 preserving the conformations described in Table 1. Also, substitution for Aib (α-Me-Ala, di-α-methyl-alanine) should limit the local conformational flexibility by two regions only, namely for −,− and +,+, the first one being compatible with conformers of Ala^{11} in Table 1. Therefore, one more desirable substitution is Aib^{11}. In Pro, the φ value is fixed at −75°; this residue is also similar to valine by its hydrophobic properties. Therefore, Val^{10} may be replaced by Pro^{10}, which adds more local conformational constraints to the UG conformers in Table 1. Replacement by Pro also requires that the preceding residue possesses only positive ψ values; Asn^{9} in Table 1 fulfills this requirement. The Pro residue already exists in the corresponding position of ST. All suggested substitutions within SEQ ID NO:1 shown below (e.g., Pro^{10}, Aib^{11} or Ala^{14}) do not change the chemical nature of the non-aliphatic amino acids (such as Asn, Asp or Thr), which may be important for the actual interaction with receptor. The former substitutions should lead only to conformational limitations shifting conformational equilibrium in UG towards the suggested "template" 3-D shape.

Based on the 3D structures defined in Table 1, a three-dimensional pharmacophore for uroguanylin was defined, enabling the determination of distances between functional groups of uroguanylin thought to directly interact with the receptor. Those groups thought to directly interact with the receptor are side groups of residues in positions 3, 5, 9 and 13 of the backbone sequence. Preferably, the residues are Glu3, Glu5, Asn9, and Thr13, as shown in SEQ ID NO:2 and SEQ ID NO:20. Thus, a three dimensional pharmacophore of uroguanylin is described in which the spatial arrangement of the four side chains of the residues at positions 3, 5, 9 and 13 may be created such that the distances between these side chains enable optional biological activity. Those distances (measured as distances between Cβ atoms of corresponding residues) are as follows: from 5.7 to 7.6 Å for the 3–5 distance, from 4.0 to 6.0 Å for 3–9; from 7.7 to 8.3 Å for 3–13, from 9.4 to from 9.4 to 9.5 Å for 5–13, and from 5.8 to 6.3 Å for 9–13.

The distances above depend only on conformations of the peptide backbone. In some cases, however, conformations of side chains themselves are also important. For instance, calculations showed that there is no conformational difference between the backbones of UG (SP301), $[Glu^{2}]$-UG (SP303), $[Glu^{3}]$-UG (SP304) and $[Glu^{2}, Glu3]$-UG (SP302) in terms of their low-energy conformations. However, there is a distinct difference in the spatial positions of the β-carboxyls of Asp and γ-carboxyls of Glu in position 3. Namely, γ-carboxyls of the Glu residues in position 3 are clearly stretched "outwards" of the bulk of the molecules farther than the corresponding β-carboxyls of the Asp residues. The above observation strongly suggests that the negatively charged carboxyl group of the side chain in position 3 specifically interacts with a positively charged binding site on the receptor; therefore, analogs containing Glu3 instead of Asp3 should be more active. At the same time, to ensure efficiency of this particular interaction, an entire system of the long-range electrostatic interactions between ligand and receptor should be well balanced. Since the Glu^{2} side chain presents more conformational possibilities compared to the Asp^{2} side chain, this balance may be slightly changed in SP302 (double substitution of Asp's for Glu's) compared to SP304 (single substitution of Asp^{3} for Glu^{3}).

Compounds capable of adopting low-energy conformations described in Table 1 are listed in Table 2. All compounds are [4,12; 7,15] bicycles.

TABLE 2

1. Parent compound: uroguanylin
(SEQ ID NO:1):
Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}

2. Compounds without modifications of cysteines:
Common sequence (SEQ ID NO:2):
Asn^{1}-Xaa^{2}-Xaa^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Thr^{13}-Xaa^{14}-Cys^{15}-Leu^{16}

where Xaa^{2} = Asp, Glu; Xaa^{3} = Asp, Glu
with the exception that Xaa^{2} and Xaa^{3} are not both Asp in same molecule
And where Xaa^{10} = Val, Pro; Xaa^{11} = Ala, Aib; Xaa^{14} = Gly, Ala

3. Compounds with mercaptoproline (Mpt) substituted for cysteine in position 7:
Common sequence (SEQ ID NO:3):
Asn^{1}-Xaa^{2}-Xaa^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Xaa^{7}-Val^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Thr^{13}-Xaa^{14}-Cys^{15}-Leu^{16}

where Xaa^{2} = Asp, Glu; Xaa^{3} = Asp, Glu
where Xaa^{10} = Val, Pro; Xaa^{11} = Ala, Aib; Xaa^{14} = Gly, Ala

4. Compounds with penicillamines (β,β-dimethylcysteines, Pen) substituted for cysteines:
Common sequence (SEQ ID NO:4):
Asn^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Glu^{5}-Leu^{6}-Xaa^{7}-Val^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Xaa^{12}-Thr^{13}-Xaa^{14}-Xaa^{15}-Leu^{16}

where Xaa^{2} = Asp, Glu; Xaa^{3} = Asp, Glu
where Xaa^{10} = Val, Pro; Xaa^{11} = Ala, Aib; Xaa^{14} = Gly, Ala
and Xaa^{4}, Xaa^{7}, Xaa^{12}, Xaa^{15} are either Cys or Pen (except not all are Cys in the same conformer)

5. Compounds with lactam bridges substituted for disulfide bridges:
Common sequence (SEQ ID NO:5):
Asn^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Glu^{5}-Leu^{6}-Xaa^{7}-Val^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Xaa^{12}-Thr^{13}-Xaa^{14}-Xaa^{15}-Leu^{16}

where Xaa^{2} = Asp, Glu; Xaa^{3} = Asp, Glu
where Xaa^{10} = Val, Pro; Xaa^{11} = Ala, Aib; Xaa^{14} = Gly, Ala
and all combinations of the following (Dpr is diaminopropionic acid):
Xaa^{4} is either Asp or Glu, and Xaa^{12} is Dpr;
Xaa^{7} is either Cys or Pen;
Xaa^{15} is either Cys or Pen;
or:
Xaa^{7} is DPr and Xaa^{15} is either Asp or Glu;
Xaa^{7} is either Asp or Glu, and Xaa^{15} is Dpr;
Xaa^{4} is either Cys or Pen;
Xaa^{12} is either Cys or Pen;

Some of the peptides shown in Table 2 contain 16 amino acid residues in which cysteine residues form disulfide bridges between Cys^{4} and Cys^{12}, and Cys^{7} and Cys^{15}, respectively. These peptides differ from the peptide sequences described in WO 01/25266, and are designed on the basis of peptide conformation and energy calculations.

In addition, peptides, varying in length from 13 to 16 amino acids, shown in Table 3, are designed, based on energy calculations and three-dimensional structures, to promote stabilization of the biologically active conformer and minimize or eliminate interconversion to biologically inactive conformers. These peptides are also designed to promote stability against proteolysis and higher temperatures. The design of these peptides involves modifications of amino acid residues that contain ionic charges at lower pH values, such as glutamic and aspartic acids.

TABLE 3

X1 Glu Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:6
X1 Glu Asp Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:7
X1 Asp Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:8
X1 Asp Asp Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:9
X1 Glu Glu Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:10
X1 Asp Glu Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:11
X1 Glu Asp Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:12
X1 Asp Asp Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:13
X1 Glu Glu Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:14
X1 Asp Glu Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:15
X1 Glu Asp Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:16

TABLE 3-continued

Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9	SEQ ID NO:17
Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys	SEQ ID NO:18
X1 Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	SEQ ID NO:19
Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu	SEQ ID NO:20
Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	SEQ ID NO:21

X1 to X9 can be any amino acid. The disulfide bridges are formed between Cys residues at 4 and 12 and between 7 and 15, respectively. SEQ ID NO:18 represents the minimum length requirement for these peptides to bind a guanylate cyclase receptor.

Pharmaceutical Compositions and Formulations

The guanylate cyclase receptor agonists of the present invention (Table 2; SEQ ID NOs:2–5 and Table 3; SEQ ID NOs:6–21), as well as uroguanylin, guanylin and/or bacterial enterotoxin ST, may be combined or formulated with various excipients, vehicles or adjuvants for oral, local or systemic administration. Peptide compositions may be administered in solutions, powders, suspensions, emulsions, tablets, capsules, transdermal patches, ointments, or other formulations. Formulations and dosage forms may be made using methods well known in the art (see, e.g., *Remington's Pharmaceutical Sciences*, 16th ed., A. Oslo ed., Easton, Pa. (1980)).

Inhibitors of cGMP-dependent phosphodiesterase may be small molecules, peptides, proteins or other compounds that specifically prevent the degradation of cGMP. Inhibitory compounds include suldinac sulfone, zaprinast, motapizone and other compounds that block the enzymatic activity of cGMP-specific phosphodiesterases. One or more of these compounds may be combined with a guanylate cyclase receptor agonist exemplified in SEQ ID NOs:2–21, uroguanylin, guanylin and *E. Coli* ST peptide.

The selection of carriers (e.g., phosphate-buffered saline or PBS) and other components suitable for use in compositions is well within the level of skill in this art. In addition to containing one or more guanylate cyclase receptor agonists, such compositions may incorporate pharmaceutically acceptable carriers and other ingredients known to facilitate administration and/or enhance uptake. Other formulations, such as microspheres, nanoparticles, liposomes, pegylated protein or peptide, and immunologically-based systems may also be used. Examples include formulations employing polymers (e.g., 20% w/v polyethylene glycol) or cellulose, or enteric formulations and pegylated peptide analogs for increasing systemic half-life and stability.

Treatment Methods

The term "treatment" refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, or preventing disease development. For a given subject, improvement in a symptom, its worsening, regression, or progression may be determined by any objective or subjective measure typically employed by one of skill in the art. Efficacy of the treatment in the case of cancer may be measured as an improvement in morbidity or mortality (e.g., lengthening of the survival curve for a selected population). Thus, effective treatment would include therapy of existing disease, control of disease by slowing or stopping its progression, prevention of disease occurrence, reduction in the number or severity of symptoms, or a combination thereof. The effect may be shown in a controlled study using one or more statistically significant criteria.

Combination therapy with one or more medical/surgical procedures and/or at least one other chemotherapeutic agent may be practiced with the invention. Other suitable agents useful in combination therapy include anti-inflammatory drugs such as, for example, steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin and the like. Prophylactic methods for preventing or reducing the incidence of relapse are also considered treatment.

Cancers expected to be responsive to compositions include breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma. Further examples of diseases involving cancerous or precancerous tissues that should be responsive to a therapeutic comprising at least one guanylate cyclase receptor agonist include: carcinoma (e.g., basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, in situ, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (e.g., B-cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytoma, histiocytosis, Hodgkin disease, non-Hodgkin lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchioma, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondroma, cylindroma, cystadenocarcinoma, cystadenoma, cystosarcoma phyllodes, dysgerminoma, ependymoma, Ewing sarcoma, fibroma, fibro-sarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor, gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangio-pericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphangioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, ostcoma, osteosarcoma, papilloma, paraganglioma, paraganglioma nonchromaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

A bolus of the inventive composition may be administered over a short time. Once a day is a convenient dosing schedule to treat, inter alia, one of the above-mentioned disease states. Alternatively, the effective daily dose may be divided into multiple doses for purposes of administration, for example, two to twelve doses per day. The dose level selected for use will depend on the bioavailability, activity, and stability of the compound, the route of administration, the severity of the disease being treated, and the condition of the subject in need of treatment. It is contemplated that a daily dosage will typically be between about 10 μg and about 2 mg (e.g., about 100 μg to 1 mg) of the compound per kilogram body weight. The amount of compound administered is dependent upon factors known to a person skilled in this art such as, for example, chemical properties of the compound, route of administration, location and type of cancer, and the like.

The subject mammal may be any animal or human patient. Thus, both veterinary and medical treatments are envisioned according to the invention.

The invention will be further described by the following non-limiting example.

EXAMPLE

Materials and Methods

Cell Culture: Human T84 colon carcinoma cells were obtained from the American Type Culture Collection at passage 52. Cells were grown in a 1:1 mixture of Ham's F-12 medium and Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 100 U penicillin/ml, and 100 μg/ml streptomycin. The cells were fed fresh medium every third day and split at a confluence of approximately 80%.

T84 cell-based assay for determining the intracellular levels of cGMP: Peptide analogs were custom synthesized by Multiple Peptide Systems, San Diego, Calif., and by Princeton Biomolecules, Langhorne, Pa. Biological activity of the synthetic peptides was assayed as previously reported (15). Briefly, the confluent monolayers of T-84 cells in 24-well plates were washed twice with 250 μl of DMEM containing 50 mM HEPES (pH 7.4), pre-incubated at 37° C. for 10 min with 250 μl of DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutylmethylxanthine (IBMX), followed by incubation with peptide analogs (0.1 nM to 10 μM) for 30 min. The medium was aspirated, and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation, and neutralization with 0.1 N NaOH, the supernatant was used directly for measurements of cGMP using an ELISA kit (Caymen Chemical, Ann Arbor, Mich.).

Results

Peptides shown in Table 4 were custom synthesized and purified (>95% purity) using a published procedure (38). Peptide analogs were evaluated in the T84 cell-based assay for their ability to enhance intracellular levels of cGMP. As shown in Table 4. SP304 (SEQ ID NO:20) gave the greatest enhancement of intracellular cGMP of all the analogs tested. SP316 (SEQ ID NO:21) was second in effectiveness, whereas the biological activities of SP301, SP302 and SP303 were all somewhat weaker. The peptide analogs SP306 and SP310 were not active in this assay. These results indicate that SP304 is the most potent peptide for enhancing cGMP. These results also suggest that the cysteine residue at position 7 cannot be substituted with penicillamine as a component of the [7.15] disulfide linkage, and that the Asn residue at position 9 cannot be changed to a Gln.

TABLE 4

Peptide agonists evaluated for biological activity in the T84 cell bioassay.

SEQ ID NO.*	Compound Code	cGMP Level** (pmol/well)
1	SP301	205
6	SP302	225
7	SP303	195
20	SP304	315
14	SP306	0
4	SP310	0
21	SP316	275

*SEQ ID's for SP301, SP304 and SP316 are the precise amino acid sequences for these analogs as given in the text.
**Intracellular cGMP level observed in T84 cells following treatment with 1 micromolar solution of the respective peptide agonist for 30 minutes. The value observed for SP304 was statistically significant with a $p > 0.5$.

To examine heat stability, 10 micromolar solutions of peptide analogs were heated at 95° C. for up to 90 minutes. At specific times during the treatment, samples were tested for their biological activity in the T84 cell-based assay. Biological activity of SP301, SP302, SP303 and SP304 did not change significantly after 60 minutes of heating. After 90 minutes, the activities of SP301, SP302 and SP303 were reduced to about 80% of their original values, whereas the biological activity of SP304 remained unaltered. This indicates that SP304 is more stable to heat denaturation compared to the other peptides tested. Based on energy calculations and 3D structure, we expected that the negatively charged carboxyl group of the side chain in position 3 of SEQ ID NO:1 specifically interacts with a positively charged binding site on the receptor. In the case where this interaction can be enhanced, analogs containing Glu3 instead of Asp3 should be more active, as was found to be the case with SP304. At the same time, to ensure efficiency of this particular interaction, an entire system of the long-range electrostatic interactions between ligand and receptor should be well balanced. Since the Glu^2 side chain presents more conformational possibilities compared to the Asp^2 side chain, this balance may be slightly changed in SP302 (double substitution of Asp's for Glu's) compared to SP304 (single substitution of Asp^3 for Glu^3). Indeed, biological activity of SP 304 is the best amongst the analogs evaluated.

Synthetic peptides SP301, SP302, SP303 and SP304 were also tested for their activities at different pH values of the T84 cell-based assay. Whereas all of these peptides showed enhanced intracellular production of cGMP at pH's ranging from 5 to 7, SP304 showed the greatest enhancement in the range between 6.5 and 7. It is important to note that the physiological pH of the large intestine is in a similar range, and, therefore, SP304 would be expected to be especially efficacious for colon cancer treatment.

We also evaluated peptides used either alone or in combination with inhibitors of cGMP dependent phosphodiesterase (e.g., zaprinast or sulindac sulfone) in T84 cell-based assays for enhancement of intracellular levels of cGMP. Combinations of an inhibitor of cGMP dependent phosphodiesterase with SP304 displayed a dramatic effect in enhancing cGMP levels in these experiments. Synthetic peptide SP304 substantially increased the cGMP level over the level reached in the presence of either zaprinast or sulindac sulfone alone. Treatment of wells with SP304 in combination with either Zaprinast or sulindac sulfone resulted in synergistic increases in intracellular cGMP levels. These increases were statistically significant, with p

values of <0.5. These data indicate that treatments combining a peptide agonist of a guanylate cyclase receptor with one or more inhibitors of cGMP dependent phosphodiesterase result in a greater than additive increase in cGMP concentrations.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to those of ordinary skill in the art that various changes and modifications can be made without departing from the spirit and scope of the invention.

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(13)
<223> OTHER INFORMATION: Any amino acid
<221> NAME/KEY: MOD_RES

-continued

<222> LOCATION: (15)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 19

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1 5 10 15

<210> SEQ ID NO 20
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide
<221> NAME/KEY: DISULFID
<222> LOCATION: (4)..(12)
<221> NAME/KEY: DISULFID
<222> LOCATION: (7)..(15)

<400> SEQUENCE: 20

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> SEQ ID NO 21
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic guanylate cyclase receptor agonist peptide
<221> NAME/KEY: DISULFID
<222> LOCATION: (2)..(10)
<221> NAME/KEY: DISULFID
<222> LOCATION: (5)..(13)

<400> SEQUENCE: 21

Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10

<210> SEQ ID NO 22
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DISULFID
<222> LOCATION: (4)..(12)
<221> NAME/KEY: DISULFID
<222> LOCATION: (7)..(15)

<400> SEQUENCE: 22

Pro Gly Thr Cys Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys
1 5 10 15

<210> SEQ ID NO 23
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Escherichia coli
<220> FEATURE:
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<222> LOCATION: (6)..(10)
<221> NAME/KEY: DISULFID
<222> LOCATION: (7)..(15)
<221> NAME/KEY: DISULFID
<222> LOCATION: (11)..(18)

<400> SEQUENCE: 23

Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr Gly Cys
Tyr
1 5 10 15

What is claimed is:

1. A peptide consisting of the amino acid sequence of SEQ ID NO:20.

2. A composition in unit dose comprising a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO:20.

3. A composition in unit dose form comprising: a) a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO: 20; and b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor, an anti-inflammatory agent, an antiviral agent and an anticancer agent.

4. The composition of either claim 2 or 3, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution and an inhalation formulation.

5. The composition of either claim 2 or 3, further comprising one or more excipients.

6. A peptide conjugate comprising polyethylene glycol (PEG) attached to a peptide consisting of the amino acid sequence SEQ ID NO:20.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

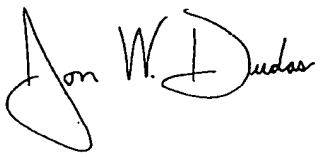
PATENT NO. : 7,041,786 B2
APPLICATION NO. : 10/107814
DATED : May 9, 2006
INVENTOR(S) : Shailubhai et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Title page item 73, the Assignee should be: "Synergy Pharmaceuticals Inc." (US).

Signed and Sealed this

Eighth Day of January, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

Please return signed/recorded to:
Pillsbury Winthrop LLP
Intellectual Property Group
1600 Tysons Boulevard
McLean, VA 22102

Atty. Dkt. PMS 284943 | M# | Client Ref.

ASSIGNMENT
of U.S. Origin Patent Application

WHEREAS, the undersigned, to wit:

1) Kunwar SHAILUBHAI
2) Gregory NIKIFOROVICH
3) Gary S. JACOB
4)
5)
6)
7)
8)

(hereinafter collectively ASSIGNOR), has/have made an invention known as Dkt.

and entitled: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

for which an application for Letters Patent of the United States

☐ was executed even date herewith and is about to be filed in the United States Patent and Trademark Office;

☒ was filed on March 28, 2002, Appln. No. 10/107,814;

AND WHEREAS Synergy Pharmaceuticals Inc.
(hereinafter ASSIGNEE), duly organized and existing under the laws of the State of DELAWARE
and having its principal office and place of business at Two Executive Drive, Suite 450, Somerset, NJ 08873
desires to acquire an interest therein:

NOW, THEREFORE, in consideration of Ten Dollars ($10.00) and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the said ASSIGNOR, does hereby sell, assign and transfer unto ASSIGNEE, its successors, assigns and legal representatives, the full and exclusive right, title and interest to the said invention in the United States and all foreign countries, as described in the aforesaid application, and to the said application and to all continuations, divisions, reissues and substitutes of said application, together with the right of priority under the International Convention for the Protection of Industrial Property, Inter-American Convention Relating to Patents, Designs and Industrial Models, and any other international agreements to which the United States of America adheres, and ASSIGNOR hereby authorizes and requests the Commissioner of Patents to issue said Letters Patent to ASSIGNEE, for its interest as ASSIGNEE, its successors, assigns and legal representatives.

PA1-114E 1/

AND ASSIGNOR hereby agrees to execute any papers requested by ASSIGNEE, its successors, assigns and legal representatives, deemed essential to ASSIGNEE's full protection and title in and to the invention hereby transferred.

ASSIGNOR furthermore agrees upon request of said ASSIGNEE, and without further remuneration, to execute any and all papers desired by said ASSIGNEE for the filing and granting of foreign applications and the perfecting of title thereto in said ASSIGNEE.

NOTE: The undersigned hereby authorizes Pillsbury Winthrop LLP of the above address to insert hereon any further identification necessary or desirable for recordation of this document.

Executed on the date(s) below indicated.

	Signature	Date Signed	Witness
1)	Name: Kunwar SHAILUBHAI	6/18/02	Lisa Osterlack
2)	Name: Gregory NIKIFOROVICH	6/19/02	Linda M. Ketchum
3)	Name: Gary S. JACOB	6/18/02	Lisa Osterlack
4)	Name:		
5)	Name:		
6)	Name:		
7)	Name:		
8)	Name:		

PAT-1146 1/0

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Kunwar Shailubhai et al.

Application No./Patent No.: 10/107,814 Filed/Issue Date: 03/28/2002

Titled: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

Synergy Pharmaceuticals Inc. a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Kunwar Shailubhai et al. To: Synergy Pharmaceuticals Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 013156, Frame 0592, or for which a copy thereof is attached.

2. From: Kunwar Shailubhai et al. To: Synergy Pharmaceuticals Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 021031, Frame 0438, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[X] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature Oct. 6 2014
Date

Gary S. Jacob, Ph.D. President and Chief Executive
Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	

Issued as 7,041,786

CONFIRMATION NO. 9117

POA ACCEPTANCE LETTER

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000071576808

Date Mailed: 10/29/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/rmturner myles/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	40737-501001US

CONFIRMATION NO. 9117

POWER OF ATTORNEY NOTICE

30623
Mintz Levin/Boston Office
One Financial Center
Boston, MA 02111

OC000000071576766

Date Mailed: 10/29/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/rmturner myles/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☒ Practitioners associated with the Customer Number: **58249**

OR

☐ Practitioner(s) named below (If more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☒ The address associated with Customer Number: **58249**

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

Synergy Pharmaceuticals Inc.
420 Lexington Avenue, Suite 2012
New York, NY 10170

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature		Date	Oct. 6, 2014
Name	Gary S. Jacob, Ph.D.	Telephone	
Title	President and Chief Executive Officer		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

American LegalNet, Inc.
www.FormsWorkflow.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208745

NDA APPROVAL

Synergy Pharmaceuticals Inc.
Attention: Evelyn Jaeger
Head of Regulatory Operations
420 Lexington Avenue, Suite 2012
New York, NY 10170

Dear Ms. Jaeger:

Please refer to your New Drug Application (NDA) dated January 29, 2016, received January 29, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trulance (plecanatide) tablets, 3 mg.

This new drug application provides for the use of Trulance (plecanatide) tablets for the treatment of chronic idiopathic constipation (CIC) in adults.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions to Section 8.1 indicated in the enclosed labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on January 3, 2017, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208745.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Trulance was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages birth to less than 2 years because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. In non-clinical studies of plecanatide, a guanylate cyclase-C (GC-C) agonist, deaths due to dehydration occurred within 24 hours in young juvenile mice. This data and the literature regarding GC-C receptor ontogeny indicate that plecanatide would not be safe to administer to pediatric patients under 2 years of age.

We are deferring submission of your pediatric studies for ages 6 years to less than 18 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. We are deferring submission of your pediatric studies for ages 2 years to less than 6 years of age because this product is ready for approval for use in adults, and pediatric studies should be delayed in this age group until additional safety data from a study evaluating GC-C receptor ontogeny and the results of the clinical studies of plecanatide in older pediatric cohorts have been evaluated. In order to avoid severe diarrhea and its serious sequelae, nonclinical data and literature findings suggest special caution should be exercised in defining the initial plecanatide dose range for young pediatric patients.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually

according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3117-1. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 12 years to less than 18 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission:	12/31/15 (completed)
Study Completion:	12/18
Final Report Submission:	02/19

3117-2. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 12 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission:	12/18
Study Completion:	12/20
Final Report Submission:	02/21

3117-3. Confirm the efficacy and safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission:	12/18
Study Completion:	12/21
Final Report Submission:	02/22

3117-4. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission:	12/20
Study Completion:	12/22
Final Report Submission:	02/23

3117-5. Confirm the efficacy and safety of Trulance (plecanatide) treatment in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission:	12/22
Study Completion:	12/25
Final Report Submission:	02/26

3117-6. Assess the long-term safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 18 years of age and have completed a confirmatory efficacy and safety study with plecanatide.

Final Protocol Submission:	02/17
Study Completion:	06/26
Final Report Submission:	08/26

Submit the protocols to your IND 74883, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient:

- to identify an unexpected serious risk of development of immune-mediated reactions with the use of Trulance (plecanatide);
- to identify unexpected serious risks related to use of Trulance (plecanatide) in the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and theoretically lead to deficiency syndromes; or
- to assess a signal of a serious potential risk of a significant fluid shift into the intestine due to age-dependent expression of the target receptor (GC-C), leading to severe

dehydration and possibly death, in pediatric patients from birth to 6 years of age exposed to a GC-C receptor agonist.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3117-7. Develop and validate a sensitive and precise assay for the detection of anti-plecanatide antibodies (ADA), including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling.

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/18

The final report should include screening, confirmation and titer assay validation reports and assay standard operating procedures (SOPs).

3117-8. Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin.

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/20

The final report should include assay validation reports and the assay standard operating procedures (SOPs).

3117-9. Develop and validate an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples taking Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/20

The final report should include assay validation report and the assay standard operating procedures (SOPs).

3117-10. A study to characterize guanylate cyclase-C (G-CC) mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients ages 0 to 6 years undergoing diagnostic gastrointestinal endoscopies as part of their medical care.

The timetable you submitted on October 13, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	04/19
Final Report Submission	07/19

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient:

- to identify an unexpected serious risk of development of immune-mediated reactions with the use of Trulance (plecanatide);
- to identify unexpected serious risks related to use of Trulance (plecanatide) in the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and theoretically lead to deficiency syndromes; or
- to identify an unexpected serious risk associated with the presence of plecanatide, or its active metabolite, in human breast milk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3117-11. Assess development of anti-drug antibody (ADA) responses in patient samples using the immunogenicity serum samples collected in the plecanatide studies (SP304203-00 and SP304203-03 and SP304203-01). Validated assays capable of sensitively and accurately detecting ADA responses, developed under PMR 3117-7, will be used. Evaluate the anti-drug antibody (ADA) rates, individual patient titers and the relationships between ADA status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 04/19

3117-12. Use the validated cross reactivity assays developed under PMR 3117-8 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between cross reactivity status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 06/20

3117-13. Use the validated neutralizing antibody assay developed under PMR 3117-9 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between neutralizing antibody status and the safety and efficacy of Trulance (plecanatide).

The timetable you submitted on November 29, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/21

3117-14. Perform a milk-only lactation trial in lactating women who have received multiple, once daily, doses of Trulance (plecanatide) therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order.

The timetable you submitted on October 13, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/17
Trial Completion:	06/18
Final Report Submission:	12/18

Submit the protocols to your IND 74883, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o)

on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling
Medication Guide
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRULANCE safely and effectively. See full prescribing information for TRULANCE.

TRULANCE (plecanatide) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

See full prescribing information for complete boxed warning.

- **TRULANCE is contraindicated in patients less than 6 years of age; in young juvenile mice, plecanatide caused death due to dehydration. (4, 8.4)**
- **Avoid use of TRULANCE in patients 6 years to less than 18 years of age. (5.1, 8.4)**
- **The safety and effectiveness of TRULANCE have not been established in patients less than 18 years of age. (8.4)**

INDICATIONS AND USAGE

TRULANCE is a guanylate cyclase-C agonist indicated in adults for treatment of chronic idiopathic constipation (CIC). (1)

DOSAGE AND ADMINISTRATION

The recommended adult dosage of TRULANCE is 3 mg taken orally once daily. (2.1)

Administration Instructions (2.2):

- Take with or without food.
- Swallow tablets whole.
- For patients who have difficulty swallowing tablets whole or those with a nasogastric or gastric feeding tube, see full prescribing information with instructions for crushing the tablet and administering with applesauce or water.

DOSAGE FORMS AND STRENGTHS

Tablets: 3 mg (3)

CONTRAINDICATIONS

- Patients less than 6 years of age due to the risk of serious dehydration. (4, 5.1, 8.4)
- Patients with known or suspected mechanical gastrointestinal obstruction. (4)

WARNINGS AND PRECAUTIONS

Diarrhea: Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate the patient. (5.2)

ADVERSE REACTIONS

Most common adverse reaction (≥2%) is diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Synergy Pharmaceuticals at 1-888-869-8869 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

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2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
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5 WARNINGS AND PRECAUTIONS
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **TRULANCE is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice administration of a single oral dose of plecanatide caused deaths due to dehydration *[see Contraindications (4), Use in Specific Populations (8.4)]*.**
- **Avoid use of TRULANCE in patients 6 years to less than 18 years of age *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.**
- **The safety and effectiveness of TRULANCE have not been established in patients less than 18 years of age *[see Use in Specific Populations (8.4)]*.**

1 INDICATIONS AND USAGE

TRULANCE is indicated in adults for the treatment of chronic idiopathic constipation (CIC).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TRULANCE is 3 mg taken orally once daily.

2.2 Preparation and Administration Instructions

- Take TRULANCE with or without food *[see Clinical Pharmacology (12.3)]*.
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- Swallow a tablet whole for each dose.
- For adult patients with swallowing difficulties, TRULANCE tablets can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube. Mixing TRULANCE crushed tablets in other soft foods or in other liquids has not been tested.

Oral Administration in Applesauce:

1. In a clean container, crush the TRULANCE tablet to a powder and mix with 1 teaspoonful of room temperature applesauce.
2. Consume the entire tablet-applesauce mixture immediately. Do not store the mixture for later use.

Oral Administration in Water:

1. Place the TRULANCE tablet in a clean cup.
2. Pour approximately 30 mL of room temperature water into the cup.
3. Mix by gently swirling the tablet and water mixture for at least 10 seconds. The TRULANCE tablet will fall apart in the water.
4. Swallow the entire contents of the tablet water mixture immediately.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 10 seconds, and swallow immediately.
6. Do not store the tablet-water mixture for later use.

Administration with Water via a Nasogastric or Gastric Feeding Tube:

1. Place the TRULANCE tablet in a clean cup with 30 mL of room temperature water.
2. Mix by gently swirling the tablet and water mixture for at least 15 seconds. The TRULANCE tablet will fall apart in the water.
3. Flush the nasogastric or gastric feeding tube with 30 mL of water using an appropriate syringe.

4. Draw up the mixture using the syringe and immediately administer via the nasogastric or gastric feeding tube. Do not reserve for future use.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 15 seconds, and using the same syringe, administer via the nasogastric or gastric feeding tube.
6. Using the same or a fresh syringe, flush the nasogastric or gastric feeding tube with at least 10 mL of water.

3 DOSAGE FORMS AND STRENGTHS

TRULANCE Tablets:

3 mg: white to off-white, plain, round tablet debossed with "SP" on one side and "3" for 3 mg on the other side.

4 CONTRAINDICATIONS

TRULANCE is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

TRULANCE is contraindicated in patients less than 6 years of age. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid-secretion into the intestines as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.

Avoid the use of TRULANCE in patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in younger mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of TRULANCE in patients 6 years to less than 18 years of age *[see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)]*.

5.2 Diarrhea

Diarrhea was the most common adverse reaction in the two placebo-controlled clinical trials. Severe diarrhea was reported in 0.6% of patients *[see Adverse Reactions (6.1)]*. If severe diarrhea occurs, suspend dosing and rehydrate the patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1733 adult patients with CIC randomized in two double-blind, placebo-controlled clinical trials (Study 1 and Study 2) to receive placebo or 3 mg of TRULANCE once daily for 12 weeks. Demographic characteristics were comparable between the TRULANCE and placebo groups *[see Clinical Studies (14)]*.

Most Common Adverse Reactions

Table 1 provides the incidence of adverse reactions reported in at least 2% of CIC patients in the TRULANCE-treated group and at an incidence that was greater than in the placebo group.

Table 1: Most Common Adverse Reactions* in Two Placebo-Controlled Trials of TRULANCE [Study 1 and Study 2] in Patients with CIC

Adverse Reaction	TRULANCE, 3 mg (N = 863) %	Placebo (N = 870) %
Diarrhea	5	1

* reported in at least 2% of TRULANCE-treated patients and at an incidence greater than placebo

Diarrhea

The majority of reported cases of diarrhea occurred within 4 weeks of treatment initiation. Severe diarrhea was reported in 0.6% of TRULANCE-treated patients compared to 0.3% of placebo-treated patients. Severe diarrhea was reported to occur within the first 3 days of treatment *[see Warnings and Precautions (5.2)]*.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 4% of TRULANCE-treated patients and 2% of placebo-treated patients. The most common adverse reaction leading to discontinuation was diarrhea: 2% of TRULANCE-treated patients and 0.5% of placebo-treated patients withdrew due to diarrhea.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of TRULANCE-treated patients and at an incidence greater than placebo were: sinusitis, upper respiratory tract infection, abdominal distension, flatulence, abdominal tenderness, and increased liver biochemical tests (2 patients with alanine aminotransferase (ALT) greater than 5 to 15 times the upper limit of normal and 3 patients with aspartate aminotransferase (AST) greater than 5 times the upper limit of normal).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration *[see Clinical Pharmacology (12.3)]* and maternal use is not expected to result in fetal exposure to the drug. The available data on TRULANCE use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of plecanatide in mice and rabbits during organogenesis at doses much higher than the recommended human dosage.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pregnant mice and rabbits were administered plecanatide during the period of organogenesis. There was no evidence of harm to embryo-fetal development at oral doses up to 800 mg/kg/day in mice and 250 mg/kg/day in

rabbits. Oral administration of up to 600 mg/kg/day in mice during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation.

The maximum recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight. Limited systemic exposure to plecanatide was achieved in animals during organogenesis (area under the plasma concentration-time curve [AUC_t] = 449 ng•h/mL in rabbits given 250 mg/kg/day). Plecanatide and its active metabolite are not measurable in human plasma following administration of the recommended clinical dosage. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

8.2 Lactation

Risk Summary

There is no information regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant. No lactation studies in animals have been conducted. Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration *[see Clinical Pharmacology (12.3)]*.

It is unknown whether the negligible systemic absorption of plecanatide by adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for serious adverse effects *[see Use in Special Populations (8.4)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRULANCE and any potential adverse effects on the breastfed infant from TRULANCE or from the underlying maternal condition.

8.4 Pediatric Use

TRULANCE is contraindicated in pediatric patients less than 6 years of age. Avoid use of TRULANCE in patients 6 years to less than 18 years of age *[see Contraindications (4), Warnings and Precautions (5.1)]*. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred within 24 hours in young juvenile mice (human age equivalent of approximately 1 month to less than 2 years) following oral administration of plecanatide, as described below in Juvenile Animal Toxicity Data. Because of increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop diarrhea and its potentially serious consequences. TRULANCE is contraindicated in patients less than 6 years of age. Given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of TRULANCE in patients 6 years to less than 18 years of age.

Juvenile Animal Toxicity Data

Single oral doses of plecanatide at 0.5 mg/kg and 10 mg/kg caused mortality in young juvenile mice on postnatal days 7 and 14, respectively (human age equivalent of approximately 1 month to less than 2 years). Treatment-related increases in the weight of intestinal contents were observed in juvenile mice following single doses of plecanatide on postnatal day 14 (human age equivalent of approximately less than 2 years), consistent with increased fluid in the intestinal lumen. Although the recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight, plecanatide and its active metabolite are not measurable in adult human plasma, whereas systemic absorption was demonstrated in the juvenile animal toxicity studies. Animal and human doses should not be compared directly for evaluating relative exposure.

8.5 Geriatric Use

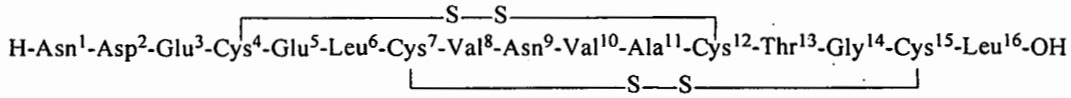
Clinical studies of TRULANCE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from patients 18 years to less than 65 years of age. Of 2601 subjects in clinical trials of TRULANCE, 273 (10%) were 65 years of age and over, and 47 (2%) were 75 years and over.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

11 DESCRIPTION

TRULANCE (plecanatide) is a guanylate cyclase-C (GC-C) agonist. Plecanatide is a 16 amino acid peptide with the following chemical name: L-Leucine, L-asparaginyl-L-α-aspartyl-L-α-glutamyl-L-cysteinyl-L-α-glutamyl-L-leucyl-L-cysteinyl-L-valyl-L-asparaginyl-L-valyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (4→12),(7→15)-bis(disulfide).

The molecular formula of plecanatide is $C_{65}H_{104}N_{18}O_{26}S_4$ and the molecular weight is 1682 Daltons. The amino acid sequence for plecanatide is shown below:



The solid lines linking cysteines illustrate disulfide bridges.

Plecanatide is an amorphous, white to off-white powder. It is soluble in water. TRULANCE tablets are supplied as a 3 mg tablet for oral administration. The inactive ingredients are magnesium stearate and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Plecanatide is structurally related to human uroguanylin, and similar to uroguanylin, plecanatide functions as a guanylate cyclase-C (GC-C) agonist. Both plecanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, plecanatide has been shown to increase fluid secretion into the gastrointestinal (GI) tract, accelerate intestinal transit, and cause changes in stool consistency.

In an animal model of visceral pain, plecanatide reduced abdominal muscle contractions, a measure of intestinal pain. The mechanism has not been studied.

12.2 Pharmacodynamics

Food Effect

Subjects who received either a low-fat, low calorie (LF-LC) meal or a high fat, high calorie (HF-HC) meal reported looser stools than fasted subjects up to 24 hours after a single dose of TRULANCE 9 mg (3 times the recommended dose). In clinical studies, TRULANCE was administered with or without food *[see Dosage and Administration (2.2)]*.

12.3 Pharmacokinetics

Absorption

Plecanatide is minimally absorbed with negligible systemic availability following oral administration. Concentrations of plecanatide and its active metabolite in plasma are below the limit of quantitation after an oral TRULANCE dose of 3 mg. Therefore, standard pharmacokinetic parameters such as AUC, maximum concentration (C_{max}), and half-life ($t_{½}$) cannot be calculated.

Food Effect

In a crossover study, 24 healthy subjects were given a single dose of TRULANCE 9 mg (3 times the recommended dose) in 3 different states: fasted; following a low-fat, low-calorie meal (LF-LC; approximately 350 calories: 17% from fat, 66% from carbohydrate, and 17% from protein); and following a high-fat, high-calorie meal (HF-HC; approximately 1000 calories: 60% from fat, 25% from carbohydrate, and 15% from protein). Plecanatide was detected in 1 subject (fasted state) at 0.5 and 1 hour post dose. Plecanatide concentrations were below the limit of quantitation for all other time points and for all other subjects. The active metabolite was not detected in any subject.

Distribution

Given that plecanatide concentrations following clinically relevant oral doses are not measurable, plecanatide is expected to be minimally distributed in tissues. Oral plecanatide is localized to the GI tract where it exerts its effects as a GC-C agonist with negligible systemic exposure. Plecanatide exhibits little to no binding to human serum albumin or human α-1-acid glycoprotein.

Elimination

Metabolism

Plecanatide is metabolized in the GI tract to an active metabolite by loss of the terminal leucine moiety. Both plecanatide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

Excretion

No excretion studies have been conducted in humans. Plecanatide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses.

Drug Interaction Studies

Neither plecanatide nor its active metabolite inhibited the cytochrome P450 (CYP) enzymes 2C9 and 3A4, and they did not induce CYP3A4 *in vitro*.

Plecanatide and its active metabolite are neither substrates nor inhibitors of the transporters P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of plecanatide was assessed in 2-year carcinogenicity studies in mice and rats. Plecanatide was not tumorigenic in mice at oral doses up to 90 mg/kg/day or in rats at oral doses up to 100 mg/kg/day. Limited systemic exposure to plecanatide was achieved at the tested dose levels in animals, whereas no detectable exposure occurred in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

Mutagenesis

Plecanatide was not genotoxic in the *in vitro* bacterial reverse mutation (Ames) assay, *in vitro* mouse lymphoma mutation assay, or the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Plecanatide had no effect on fertility or reproductive function in male or female mice at oral doses of up to 600 mg/kg/day.

14 CLINICAL STUDIES

The efficacy of TRULANCE for the management of symptoms of CIC was established in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients (Study 1 and Study 2). In the Intention-to-Treat (ITT) population, a total of 905 patients (Study 1) and 870 patients (Study 2) were randomized 1:1 to either placebo or TRULANCE 3 mg, once daily. In clinical studies, study medication was administered without respect to food intake. Demographics for these studies included an overall mean age of 45 years (range 18 to 80 years), 80% female, 72% white, and 24% black.

To be eligible for the studies, patients were required to meet modified Rome III criteria for at least 3 months prior to the screening visit, with symptom onset for at least 6 months prior to diagnosis. Rome III criteria were modified to require that patients report less than 3 defecations per week, rarely have a loose stool without the use of laxatives, not use manual maneuvers to facilitate defecations, and not meet criteria for IBS-C. In addition, patients were required to report at least two of the following symptoms:

- Straining during at least 25% of defecations
- Lumpy or hard stool in at least 25% of defecations
- Sensation of incomplete evacuations for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations

Patients who met these criteria were also required to demonstrate the following during the last 2 weeks of the screening period:

- Less than 3 complete spontaneous bowel movements (CSBMs) (a CSBM is an SBM that is associated with a sense of complete evacuation) in each of the two weeks
- Bristol Stool Form Scale (BSFS) of 6 or 7 in less than 25% of spontaneous bowel movements (SBMs) (an SBM is a bowel movement occurring in the absence of laxative use)
- One out of the following three:
    - BSFS of 1 or 2 in at least 25% of defecations
    - A straining value recorded on at least 25% of days when a BM was reported
    - At least 25% of BMs result in a sense of incomplete evacuation

The efficacy of TRULANCE was assessed using a responder analysis and change-from-baseline in CSBM and SBM endpoints. Efficacy was assessed using information provided by patients on a daily basis in an electronic diary.

A responder was defined as a patient who had a least 3 CSBMs in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study. The responder rates are shown in Table 2.

Table 2: Efficacy Responder Rates in the Two Placebo Controlled Studies of CIC: at least 9 of 12 weeks and at least 3 of the last 4 weeks (ITT Population)

Study 1			
	TRULANCE 3 mg N = 453	**Placebo N = 452**	**Treatment Difference[#] [95% CI*]**
Responder[^]	21%	10%	11% [6.1%, 15.4%]
Study 2			
	TRULANCE 3 mg N = 430	**Placebo N = 440**	**Treatment Difference[#] [95% CI*]**
Responder[^]	21%	13%	8% [2.6%, 12.4%]

* CI = confidence interval

^ primary endpoint defined as a patient who had a least 3 CSBMs in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study

p-value <0.005

In both studies, improvements in the frequency of CSBMs/week were seen as early as week 1 with improvement maintained through week 12. The difference between the TRULANCE group and the placebo group in the mean change of CSBMs/week frequency from baseline to week 12 was approximately 1.1 CSBMs/week.

Over the 12 week treatment period, improvements were observed in stool frequency (number of CSBMs/week and SBMs/week) and/or stool consistency (as measured by the BSFS), and/or in the amount of straining with bowel movements (amount of time pushing or physical effort to pass stool) in the TRULANCE group as compared to placebo.

Following completion of the study drug treatment period, patients continued to record data in the daily diary for a 2 week Post-Treatment Period. During this time, TRULANCE-treated patients generally returned to baseline for these study endpoints.

In Studies 1 and 2, a third randomized treatment arm of TRULANCE 6 mg once daily did not demonstrate additional treatment benefit and had a greater incidence of adverse reactions than TRULANCE 3 mg once daily. Therefore, TRULANCE 6 mg once daily is not recommended *[see Dosage and Administration (2.1)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRULANCE tablets are packaged in an aluminum foil unit dose blister pack of 30 in a child-resistant pack or in a white, opaque, high-density polyethylene round bottle with a screw-top polypropylene child-resistant cap and heat-activated induction seal. Each bottle container-closure system also contains a desiccant and a polyester coil.

TRULANCE 3 mg tablets are white to off-white, plain and round, debossed with "SP" on one side and "3" for 3 mg on the other side and supplied as:

NDC Number	Size
70194-203-30	Bottle of 30
70194-003-30	Aluminum foil unit dose blister pack of 30 in a child-resistant pack

Store at room temperature, 20 to 25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Keep TRULANCE in a dry place. Protect from moisture. For bottles, keep TRULANCE in the original bottle. Do not remove desiccant from the bottle. Do not subdivide or repackage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise Patients:

Diarrhea

To stop TRULANCE and contact their healthcare provider if they experience severe diarrhea *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of TRULANCE in children, especially in children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to take steps to store TRULANCE securely and out of reach of children and to dispose of unused TRULANCE *[see Contraindications (4), Warnings and Precautions (5.2)]*.

Administration and Handling Instructions

- To take TRULANCE once daily with or without food *[see Dosage and Administration (2.2)]*.
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- To swallow TRULANCE tablets whole.
- If adult patients have swallowing difficulties, TRULANCE tablets can be crushed and administered orally in either applesauce or with water, or administered with water via a nasogastric or gastric feeding tube, as described in the Medication Guide.
- To keep TRULANCE in a dry place. Protect from moisture. For bottles, keep TRULANCE in the original bottle. Do not remove desiccant from the bottle. Do not subdivide or repackage. Remove and discard polyester coil after opening. Keep bottles closed tightly *[see How Supplied/Storage and Handling (16)]*.

TRULANCE™ is a trademark of Synergy Pharmaceuticals Inc.

Manufactured for:
Synergy Pharmaceuticals Inc.
420 Lexington Avenue, Suite 2012
New York, New York 10170

Medication Guide
TRULANCE™ (troo' lans)
(plecanatide) tablets

What is the most important information I should know about TRULANCE?

- **Do not give TRULANCE to children who are less than 6 years of age. It may harm them.**
- **You should not give TRULANCE to children 6 years to less than 18 years of age. It may harm them.**

See **"What are the possible side effects of TRULANCE?"** for more information about side effects.

What is TRULANCE?

TRULANCE is a prescription medicine used in adults to treat a type of constipation called chronic idiopathic constipation (CIC). Idiopathic means the cause of the constipation is unknown.

It is not known if TRULANCE is safe and effective in children less than 18 years of age.

Who should not take TRULANCE?

- **Do not give TRULANCE to children who are less than 6 years of age.**
- Do not take TRULANCE if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Before taking TRULANCE, tell your doctor about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if TRULANCE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TRULANCE passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take TRULANCE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take TRULANCE?

- Take TRULANCE exactly as your doctor tells you to take it.
- Take TRULANCE by mouth, 1 time each day with or without food.
- If you miss a dose, skip the missed dose. Take the next dose at your regular time. Do not take 2 doses at the same time.
- TRULANCE tablets should be swallowed whole.
  - Adults who cannot swallow TRULANCE tablets whole may crush the TRULANCE tablet and mix with applesauce or dissolve TRULANCE in water before swallowing. TRULANCE tablets may also be taken with water by adults through a nasogastric or gastric feeding tube.

It is not known if TRULANCE is safe and effective when crushed and mixed with other foods or dissolved in other liquids.

Taking TRULANCE in applesauce:

- Crush the TRULANCE tablet in a clean container until it is a powder and mix with 1 teaspoon of room temperature applesauce.
- Swallow all of the TRULANCE and applesauce mixture right away. Do not keep the TRULANCE and applesauce mixture for future use.

Taking TRULANCE in water:

- Place the TRULANCE tablet in a clean cup and pour 1 ounce (30 mL) of room temperature water into the cup.
- Gently swirl the TRULANCE tablet and water for at least 10 seconds. The TRULANCE tablet will fall apart in the water.
- Swallow all of the TRULANCE tablet and water mixture right away. Do not keep the mixture for

future use.

- If you see any part of the tablet left in the cup, add another 1 ounce (30 mL) of water to the cup, swirl for at least 10 seconds, and swallow right away.

Taking TRULANCE through a nasogastric or gastric feeding tube:

Gather the supplies you will need to take your TRULANCE dose. Your doctor should tell you what size catheter tipped syringe you will need for your dose. Ask your doctor if you have any questions about how to give TRULANCE the right way.

- Place the TRULANCE tablet in a clean cup with 1 ounce (30 mL) of room temperature water.
- Gently swirl the TRULANCE tablet and water for at least 15 seconds. The TRULANCE tablet will fall apart in the water.
- Flush the nasogastric or gastric feeding tube with 1 ounce (30 mL) of water.
- Draw up the TRULANCE tablet and water mixture into a catheter tipped syringe and give right away through the nasogastric or gastric feeding tube. Do not keep the mixture for future use.
- If you see any part of the tablet left in the cup, add another 1 ounce (30 mL) of water to the cup, swirl for at least 15 seconds and use the same catheter tipped syringe to give the mixture through the nasogastric or gastric feeding tube.
- Using the same or another catheter tipped syringe, flush the nasogastric or gastric feeding tube with at least 10 mL of water.

What are the possible side effects of TRULANCE?

TRULANCE can cause serious side effects, including:

- See **"What is the most important information I should know about TRULANCE?"**
- **Diarrhea is the most common side effect of TRULANCE, and it can sometimes be severe.**
  - Diarrhea often begins within the first 4 weeks of TRULANCE treatment.

Stop taking TRULANCE and call your doctor if you develop severe diarrhea.

These are not all the possible side effects of TRULANCE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRULANCE?

- Store TRULANCE at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TRULANCE in a secure place and in the bottle or blister pack that it comes in.
- The TRULANCE bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.
- The TRULANCE bottle contains a polyester coil to help protect the tablets during shipping. Remove the polyester coil from the bottle and throw it away when you are ready to start taking TRULANCE.
- Keep the container of TRULANCE tightly closed and in a dry place.
- Safely throw away TRULANCE that is out of date or no longer needed.

Keep TRULANCE and all medicines out of the reach of children.

General information about the safe and effective use of TRULANCE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRULANCE for a condition for which it was not prescribed. Do not give TRULANCE to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your doctor or pharmacist for information about TRULANCE that is written for health professionals.

What are the ingredients in TRULANCE?

Active ingredient: plecanatide
Inactive ingredients: magnesium stearate and microcrystalline cellulose

TRULANCE™ is a trademark of Synergy Pharmaceuticals Inc.

Manufactured for:
Synergy Pharmaceuticals Inc.
420 Lexington Avenue, Suite 2012
New York, New York 10170

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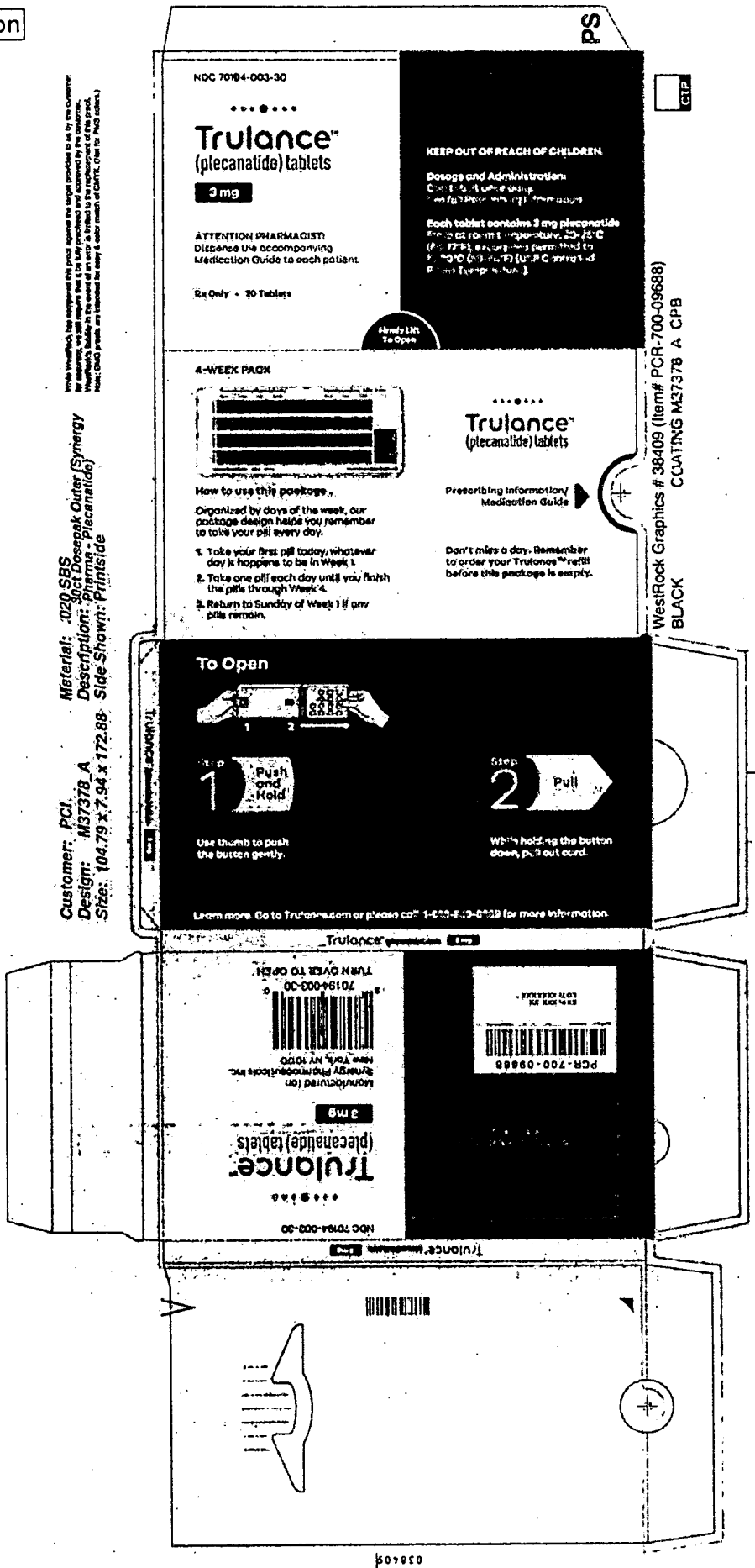
For more information, go to www.synergypharma.com or call 1-888-869-8869.

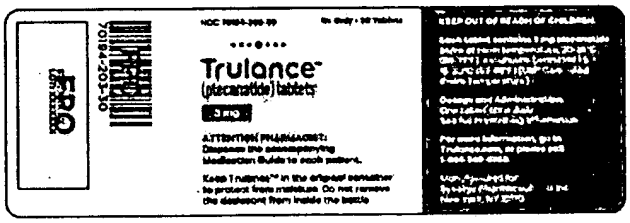
This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 01/2017

30CT Outer Carton

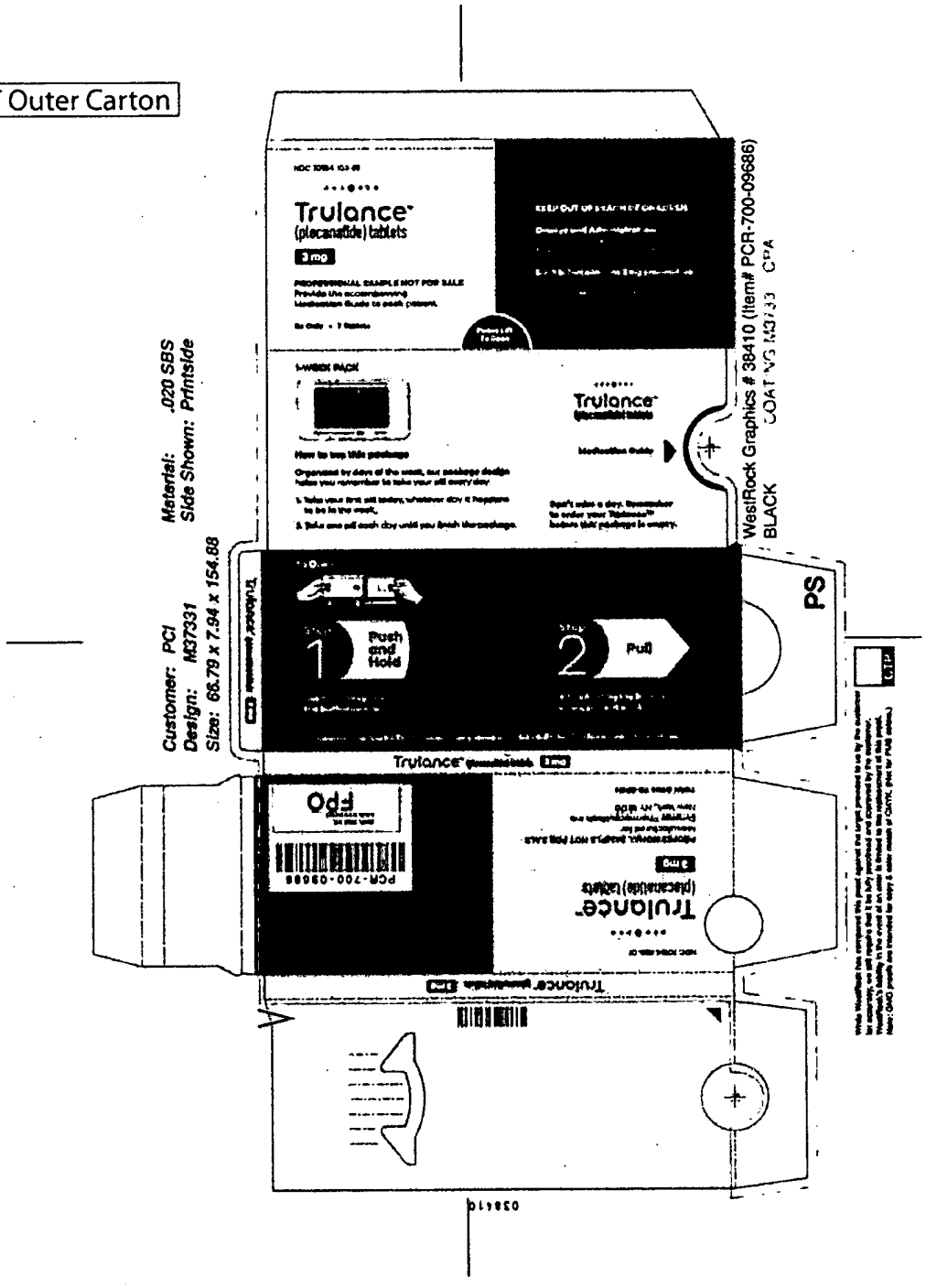


Reference ID: 4044252

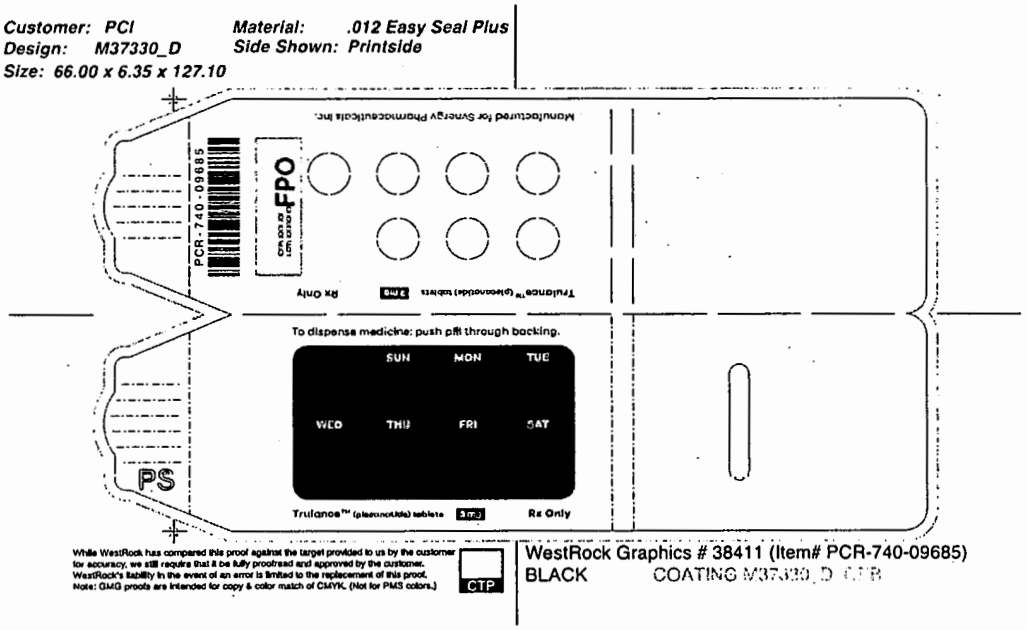
30CT Bottle Sticker



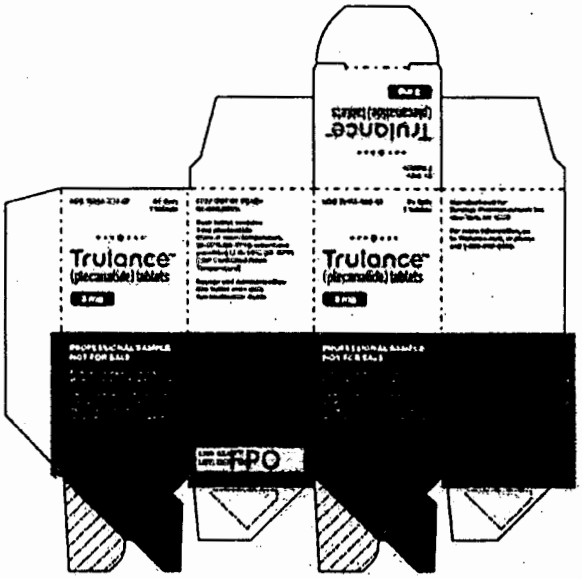
7CT Outer Carton



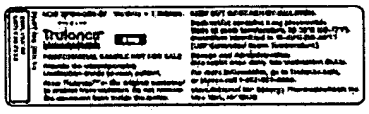
7CT Blister Pack



7CT Bottle Box



7CT Bottle Sticker



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/s/

JULIE G BEITZ
01/19/2017

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Date	Serial No. / Interaction	Description
April 13, 2006	N/A - 01	Request for a type B pre-IND meeting for SP-304 (guanilib) for the treatment of ulcerative colitis and Crohn's Disease. Sent to the attention of Brian Strongin (Document Control Room). The cover letter was dated April 13, 2006, and was received by FDA on April 14, 2006.
April 21, 2006	N/A - 02	Fax received from Kristin Everett (regulatory project manager), Division of Gastroenterology Products, granting pre-IND meeting request and confirming Type B meeting for PIND 74,883 (assigned to SP-304) for discussion of clinical and nonclinical issues. Date if meeting is June 15, 2006, from 3 PM to 4 PM (EST). Location of meeting is White Oak Campus, 10903 New Hampshire Ave, Silver Spring, MD 20993. Background info package to be received by FDA by May 16th. FDA wants 3 copies submitted to IND and 8 desk copies sent to Kristin Everett. Request diskette (CD) with Word document with the pre-IND meeting package containing 2 files: 1) list of firm's attendees, and 2) specific questions to be answered at the meeting.
May 10, 2006	N/A - 03	Pre-IND Meeting Information Package sent to FDA by FedEx for their receipt May 11, 2006. Package included 3 IND copies (1 each of red, orange, green binders) and 8 plain (desk) copies along with a CD containing 2 files: 1 with names of attendees from Synergy, and 1 with the questions. CD was scanned using Norton software to assure virus-free status.
May 15, 2006	N/A - 04	Kristen Everett calls Don and inquires about the meeting information package and Word files, which she had not received yet. Kristen requested these files to be sent as soon as possible.
May 16, 2006	N/A - 05	Don sends an E-mail Kristen Everett containing the meeting information package (Adobe pdf), tracking information (Adobe pdf), and two Word files (meeting attendees and list of questions). Don followed up the E-mail with a phone call prior to noon, at which time Kristen informed Don that package was delivered to her office this morning and she has everything. Kristen confirmed that the meeting is still on for June 15th. Kristin also indicated that they would probably have comments before the meeting to Synergy.
June 12, 2006	N/A - 06	FDA (from Kristin Everett) sends answers to questions by fax (4 pages) to Don Picker (2 days prior to scheduled meeting).
June 13, 2006	N/A - 07	Synergy canceled the pre-IND meeting after receiving FDA's responses to Synergy's questions by fax.

Date	Serial No. / Interaction	Description
June 29-30, 2006	N/A - 08	As a result of FDA's responses to the exploratory pre-IND submission, Synergy revised the IND filing strategy for SP-304 to submit a traditional IND to the FDA. Second request sent by FedEx for a type B pre-IND meeting for SP-304 (guanilib) via a traditional IND pathway this time (not exploratory IND pathway) for the treatment of ulcerative colitis and Crohn's Disease was sent. Sent 3 copies in blue binders on June 29, 2006 to the attention of Kristin Everett, RN, Regulatory Project Manager (Document Control Room). The cover letter was dated June 30, 2006, and was received by FDA on June 30, 2006.
July 13, 2006	N/A - 09	Fax received by Synergy (Don Picker) dated July 13, 2006 granting a Type B pre-IND meeting (teleconference) to discuss the traditional IND for SP-304 (guanilib). Meeting will be Friday, Sept. 8, 2006 from 10 AM to 11 AM EST at the White Oak Campus, 10903 New Hampshire Ave, Silver Spring, MD 20993. FDA wants 3 IND copies and 7 desk copies at least 30 days prior to the meeting (by Aug 9th 2006). FDA also wants a disk or email with two separate Word files: 1) List of firm's attendees with titles, and 2) specific questions to be answered at the meeting.
July 26, 2006	N/A - 10	Pre-meeting information package (the requested number of copies indicated above) and CD with Word files sent to FDA to the attention of Kristin Everett.
September 5, 2006	N/A - 12	Don Picker receives draft answers from FDA sent as a fax to questions posed in the pre-IND meeting submission.
September 7, 2006	N/A - 13	Don Picker calls Kristin Everett and confirms that the meeting is still on for September 8th, asks for the teleconference to be delayed a little in the day to allow FDA time to review a fax and email from Synergy with more information on Question 6 (sent by fax to Kristin Everett on September 7th around 4:30 PM.
September 8, 2006	N/A - 14	Pre-IND meeting with FDA starting at 10 AM. Lasted approximately 35 minutes. Primary points of discussion were clarification of the answers to Questions 1 and 6 of the non-clinical questions posed in the pre-IND meeting package.
September 11, 2006	N/A - 15	Don receives a request from FDA for names and organizations of the Synergy teleconference participants (Sept. 8, 2006). Don faxed back the completed meeting roster back to FDA containing the names of the 4 participants from Synergy on the call (Don Picker, Shailu, Katie Colgate, and Rita O'Neil)

Date	Serial No. / Interaction	Description
October 3, 2006	N/A - 16	FDA official meeting minutes from the Sept. 8, 2006 meeting are received, signed electronically by Kristin Everett (Project Manager) and John Hyde (Medical Team Leader) at the Division of Gastroenterology Drug Products. In the minutes, FDA notes that Synergy is responsible for notifying them of "any significant differences in understanding regarding the meeting outcomes". The minutes include the original answers to the questions received on Sept. 4, 2006, along with a summary of additional discussion that occurred at the meeting with respect to Questions 1 and 6.
April 2, 2008	0000	Original IND filing for SP-304
April 2, 2008	N/A - 17	Gary Jacob sends email to Brian Strongin at FDA, Supervisory Project Manager, Division of Gastroenterology Products, asking status of IND
May 2, 2008	N/A - 18	Email received from Matthew Scherer indicating the IND has been approved.
May 23, 2008	0001	Protocol Version 2 Amendment No.1 for Protocol No. SP-SP304101-08 dated May 2, 2008
May 29, 2008	n/a	74,883 IND Acknowledgement Letter
June 27, 2008	0002	Protocol Version 2 Amendment No.2 for Protocol No. SP-SP304101-08 dated May 30, 2008
July 11, 2008	0003	Protocol Version 2 Amendment No.3 for Protocol No. SP-SP304101-08 dated June 27, 2008
November 3, 2008	0004	Provide additional non-clinical data to support request to lower max dose of GLP monkey study to 75/mg/kg for repeat dose IND
February 20. 2009	N/A - 23	FDA response to November 3, 2008 request to lower max dose of GLP monkey study to 75/mg/kg for repeat dose IND
March 4, 2009	N/A - 24	FDA places SP-304 on partial clinical hold until repeat dose animal data is submitted and reviewed prior to starting any repeat dose studies in humans
June 17, 2009	0005	2009 Annual Report
January 4, 2010	N/A - 26	E-mail communication with FDA PM to let him know that the Complete Response to the Clinical Hold would be submitted with 28-day tox reports under Serial No. 0006 and that we would submit the Phase IIa protocol and Phase I HV CSR under Serial No. 0007 on January 7, 2010
January 7, 2010	0006	Submit audited draft 28-Day Toxicology Study reports (monkey mouse, and pilot mouse)
January 7, 2010	0007	Submit SP-SP304101-08 HV CSR and SP-SP304201-09 Phase IIa protocol

Date	Serial No. / Interaction	Description
January 8, 2010	N/A - 29	E-mail communication with FDA PM to confirm IND Amendment Serial No. 0006 and 0007 were both sent for delivery on January 8, 2010 (including the requested 2 desk copies of each IND amendment.
February 5, 2010	N/A - 30	FDA letter removing the partial clinical hold
February 24, 2010	0008	Submit SP-304201-09 Protocol Amendments 1 and 2, IB version 2 dated 02-22-10, Investigator information for Investigators participating in the SP-SP304201-09 clinical trial and to submit update to Section 7 of the IND (CMC)
April 28, 2010	0009	Submit SP-304201-09 Protocol Amendment 3 and updated Investigator information for Investigators participating in the SP-SP304201-09 clinical trial
June 16, 2010	0010	Submit FINAL 28-Day Toxicology Study reports (monkey and mouse)
June 17, 2010	0011	2010 Annual Report
July 8, 2010	0012	Chemistry, Manufacturing and Control (CMC) Information Amendment: CMC information for the 0.3 mg dosage strength SP-304 drug product (API in capsules) manufactured for use in the phase 2a clinical study (Protocol No. SP-SP304201-09)
July 26, 2010	N/A - 36	E-mail to Matthew Scherer (Regulatory Project Manager) from Cliff Chyatte providing contact information
August 6, 2010	0013	Request for a type C meeting with FDA to obtain guidance and seek agreement on the development and validation plan to demonstrate that the patient-reported outcome (PRO) instruments to support labeling claims are fit for purpose for use in the SP-304 (plecanatide) clinical program
August 20, 2010	N/A - 38	E-mail from Matthew Scherer indicating that FDA has granted Synergy's request for a meeting to discuss our PRO instrument validation plan.
Sept 10, 2010	N/A - 39	Letter from Matthew Scherer confirming that FDA has granted Synergy's request for a meeting to discuss our PRO instrument validation plan, and stipulating that the meeting has been scheduled for December 6, 2010.
October 7, 2010	0014	Clinical Information Amendment: Investigator Data for Protocol No. SP-SP304201-09
November 5, 2010	0015	Briefing Materials for a Type C meeting with FDA on December 6, 2001 to discuss Synergy's patient-reported outcome (PRO) development and validation plans
November 5, 2010	N/A - 41	Six (6) desk copies to Matthew Scherer of Briefing Materials for a Type C meeting with FDA on December 6, 2001 to discuss Synergy's patient-reported outcome (PRO) development and validation plans

November 10; 2010	0016	Final, audited study reports for segment II reproductive toxicity studies of SP-304 in rabbits (Study No. 20003036) and in mice (Study No. 20001133)
November 19, 2010	N/A - 44	E-mail from Matthew Scherer to Gary Jacob requesting an electronic copy of the Briefing Materials for the upcoming meeting with FDA
November 19, 2010	N/A - 45	E-mail from Cliff Chyatte to Matthew Scherer providing an electronic copy of the Briefing Materials for the upcoming meeting with FDA
November 19, 2010	N/A - 46	E-mail from Matthew Scherer to Cliff Chyatte confirming the receipt of an electronic copy of the Briefing Materials for the upcoming meeting with FDA
November 29, 2010	N/A - 47	E-mail from Cliff Chyatte to Matthew Scherer providing a list of anticipated participants and dial-in information for the upcoming meeting with FDA
December 2, 2010	N/A - 48	E-mail from Matthew Scherer to Cliff Chyatte providing FDA's preliminary response to our meeting questions
December 2, 2010	N/A - 49	Letter from Matthew Scherer containing FDA's preliminary comments on our meeting questions
December 3, 2010	N/A - 50	E-mail from Cliff Chyatte to Matthew Scherer providing replacement materials for Appendix A of the Briefing Book that was previously provided as part of the briefing materials for the FDA meeting
December 13, 2010	N/A - 51	E-mail from Cliff Chyatte to Matthew Scherer providing Synergy Pharmaceuticals' meeting minutes for a Type C meeting with FDA that took place as a teleconference on December 6, 2010 and discussed Synergy's patient-reported outcome (PRO) development and validation plans in support of labeling claims for SP-304 (plecanatide).
December 14, 2010	0017	Synergy Pharmaceuticals' meeting minutes for a Type C meeting with FDA that took place as a teleconference on December 6, 2010 and discussed Synergy's patient-reported outcome (PRO) development and validation plans in support of labeling claims for SP-304 (plecanatide).
January 5, 2011	N/A - 52	FDA's meeting minutes for a Type C meeting with FDA that took place as a teleconference on December 6, 2010 and discussed Synergy's patient-reported outcome (PRO) development and validation plans in support of labeling claims for SP-304 (plecanatide).
July 15, 2011	0018	Form 1571 and Letter stating intent to change to electronic submissions- Octagon
July 15, 2011	0019	2011 IND Annual Report
August 23, 2011	0020	13-Week Toxicology Study Reports- Mice and Monkey
August 29, 2011	0021	Investigator Brochure Version 4.3 Dated 8/23/11 Delegation of Authority Synergy to Parexel (with 1571)
September 7, 2011	0022	Protocol SP30420210, ePRO dossier, summary of supporting documentation, 1571 and Delegation of Authority to Parexel
September 20, 2011	0023	Final Study Report for Phase IIa study with mention of dose selection for Study SP 304 202-09 CSR
September 23, 2011	0024	Protocol Amendment: New Investigators - Drs. Cyzner (CTRN 073), Fogel (CTTN 121), Fowler (CTRN 122), Gonzalez (CTRN 149), Horn (CTRN 182), Huffman (CTRN 184), Levinsky (CTRN 245), Lubin (CTRN 253), Medoff (CTRN 274), Ringold (CTRN 351), Schneider (CTRN 369), Wiltz (CTRN 438), Choi (CTRN 449)

September 23, 2011	N/A - 53	Email from L. Barrow to M. Scherer @ FDA with attachment for Serial 0025 (see Serial #0025 below)
September 23, 2011	0025	General Correspondence - Other; US IND Agent Appointment (Michael Kim PAREXEL will submit and receive correspondence on technical and administrative matters on behalf of Synergy
October 6, 2011	0026	Protocol Amendment: New Investigators - Drs. Bennett (CTRN 028), Blumenau (CTRN 036), Campbell (CTRN 048), Clark (CTRN 063), Diaz (CTRN 088), Karn (CTRN 206), Moussa (CTRN 297), Paddu (CTRN 316), Patel (CTRN 321), Taormina (CTRN 410), Varunok (CTRN 426).
October 12, 2011	0027	Protocol Amendment: New Investigators - Drs. Dawson (CTRN 080), Egelhof (CTRN 103), Glover (CTRN 141), Gonte (CTRN 148), Gupta (CTRN 157), Klein (CTRN 220), Perez (CTRN 325), Wiener (CTRN 435).
October 20, 2011	N/A - 54	New Contact for IND, Review of New Protocol
October 21, 2011	0028	Information Amendment: CMC Information. GMP drug substance batch 101221; drug product lots 2011F101A, 2011099A, 2011F100A (new mfg., production method, release testing and COA. GMP placebo drug product lot 2011F096A - new mfg., release & COA.
October 25, 2011	0029	Protocol Amendment: New Investigators - Drs. Barish (CTRN 019), Dimitroff (CTRN 089), Ervin (CTRN 110), Gasic (CTRN 130), Hoekstra (CTRN 178), Kaplan (CTRN 203), Koltun (CTRN 224), Krause (CTRN 227), Kuettel (CTRN 230), Velazquez (CTRN 259), Marcadis (CTRN 260), Oberoi (CTRN 311), Padilla (CTRN 317), Schwartz (CTRN 373), Serje (CTRN 378), Surowitz (CTRN 408), Wakefield (CTRN 431), Prince (CTRN 454).
November 2, 2011	0030	Information Amendment - Clinical Protocol Amendment to submit SAIRB approved protocol SP304-20210 V2.0 dated 25 Oct 2011 completed by US Agent PXL.
November 4, 2011	0031	Protocol Amendment - New Investigators: Drs. Allen (CTRN 003), Danzig (CTRN 075), Goldstein (CTRN 147), Holmes (CTRN 179), Jo (CTRN 195), Kirstein (CTRN 217), Balakrishnan (CTRN 390).
November 22, 2011	0032	Protocol Amendment - New Investigators: Drs. Andrews (CTRN 008), Call (CTRN 046), Cha (CTRN 054), Curtis (CTRN 071), DeLuca (CTRN 084), Ennis (CTRN 106), Naccarato (CTRN 303), and Smith (CTRN 456).
December 2, 2011	0033	Protocol Amendment - New Investigators: Drs. Baber (CTRN 014), Belingar (CTRN 459), Ferrera (CTRN 117), Grossman (CTRN 155), Hellstern (CTRN 450), and LaFata (CTRN 234).
December 9, 2011	0034	Protocol Amendment - New Investigators: Drs. Barclay (CTRN 018), DuPree (CTRN 098), Johnson (CTRN 197), Karnam (CTRN 302), Menn (CRTN 278), Rosell (CTRN 355), and Trate (CTRN 418).
December 16, 2011	0035	Protocol Amendment - New Investigators: Drs. Beyer (CTRN 030), Johnson (CTRN 198), Shah (CTRN 380), Liakos (CTRN 463), and Forde (CTRN 464).
December 23, 2011	0036	Protocol Amendment - New Investigators: Drs. Bala (CTRN 016), Hale (CTRN 161), Jasper (CTRN 193), Moparty (CTRN 293), Alapati (CTRN 314), Tieman (CTRN 416), and Turner (CTRN 420).
January 6, 2012	0037	Protocol Amendment - New Investigators: Drs. Ahuja (CTRN 002), Ben-Zvi (CTRN 026), Fein (CTRN 115), Kneller (CTRN 222), McGuire (CTRN 237), Sligh (CTRN 392), and Souder (CTRN 395).
January 24, 2012	0038	General Correspondence - Change of US Agent to Synergy
February 3, 2012	0039	Information Amendment - Pharmacology/Toxicology to submit Study of Fertility and Early Embryonic Development to Implantation of Plecanatide by Oral Gavage in Mice (Study No.20016090, dated 20 January 2012).
February 7, 2012	0040	Protocol Amendment: New Investigators - Dr. Faruqui (CTRN 466), Dr. Granda (CTRN 151), Dr. Gross (CTRN 154), Dr. Harris (CTRN 168), Dr. Iyer (CTRN 467), Dr. Lumicao (CTRN 460), Dr. Reyes (CTRN 347), Robles-Pena (CTRN 462).

February 9, 2012	0041	Information Amendment - Pharmacology/Toxicology Final Study Reports 1) *Bacterial Reverse Mutation Assay* (Study No. AD27SJ.503.BTL, dated 26 January 2012), and 2) *In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay)* (Study No. AD27SJ.704.BTL, dated 24 January 2012).
February 28, 2012	0042	Information Amendment - Pharmacology/Toxicology to submit Final Study Report for Mouse Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of Plecanatide (SP-304), Study No. AD27SJ.123.BTL dated 21 February 2012.
March 20, 2012	0043	Protocol Amendment: New Investigators - Drs. Ayub (CTRN 013), Bretton (CTRN 225), Sellers (CTRN 375) and Singh (CTRN 079)
March 22, 2012	0044	General Correspondence - Request for Type C Meeting for IBS-C
March 26, 2012	n/a	Phone message received from M. Scherer (also see April 2, 2012 email voicemsg.wav correspondence below.
March 27, 2012	n/a - 55	Email Correspondence from B. Strongin FDA to establish a Pre-IND to archive the IBS-C submission and to withdraw Serial 0044 Request for Type C meeting under IND 74,883.
March 28, 2012	0045	General Correspondence - Form FDA 1571, box 15 revised to Dr. Steven Caras as person responsible for review of safety for plecanatide.
April 2, 2012	n/a	Email communication to M. Scherer Response to 26 March phone message and status update of CIC study.
April 3, 2012	n/a - 56	Email response from M. Scherer to withdraw the Type C meeting request with a formal submission to the IND.
April 4, 2012	0046	General Correspondence - Withdrawn request for Type C Meeting for IBS-C (see SS #0044)
April 19, 2012	0047	General Correspondence -Type C Meeting Request to discuss the Approach for Selecting the High Dose of Plecanatide in the Planned Carcinogenicity Studies
April 30, 2012	0048	New Investigators - Drs. Finnegan (CTRN 470), Maynard (CTRN 468), and Ibarra (CTRN 188)
May 9, 2012	0049	IND Safety Report Initial MFR Report no. 2012US001277, 1571, MedWatch Report
May 29, 2012	n/a - 57	FDA Correspondence (SS 0047) Type C Meeting Request Granted for July 25, 2012.
June 1, 2012	0050	IND Safety Report Follow-Up To A Written Report no 2012US001277, 1571, MedWatch Report
June 25, 2012	0051	General Correspondence - Type C Meeting package (see FDA correspondence of May 29, 2012 and serial submission 0047 for details).
June 27, 2012	0052	New Investigator, Drs. Friedenberg (CTRN 469), Espinoza (CTRN 355), Bargar (CTRN 481), Brown (CTRN 479), Dorn (CTRN 092), Stamatin (CTRN 473)
June 29, 2012	0053	Annual Report 2012 - Compilation cut-off May 1, 2012
July 13, 2012	0054	CMC capsules stability at room temperature
July 17, 2012	n/a - 58	Email communication to M Scherer List of Synergy Participants for July 25, 2012 meeting Email communication to M Scherer Word version of questions for the Type C meeting July 25, 2012
July 19, 2012	n/a - 59	Email communication Attachment from M. Scherer. Meeting Preliminary Comments (carc study)
July 20, 23 and 24, 2012	n/a - 60	Email communication to M Scherer from Gary Jacob regarding cancellation of July 25 meeting, and SPA for carc study. Email

		communication from M Scherer to Gary Jacob regarding cancellation of July 25 meeting and SPA for carc study.
July 27, 2012	0055	New Investigators, Drs. Yong (474) and House (475)
October 4, 2012	0056	Information Amendment - Pharm/Tox: Plecanatide - 26 Week Oral Tox Study in Mice with a 4-wk Recovery
October 18, 2012	0057	Information Amendment - CMC for new drug product tablet dosage.
November 5, 2012	0058	Information Amendment: Chemistry, manufacturing, and Control (CMC) information
November 9,2012	0059	General Correspondence - Other Notification of Pending Carcinogenicity Protocol Submission for SPA.
November 21, 2012	0060	Information Amendment - Clinical. Submission of bioanalytical reports including Pxyant Rpt 1902 (12.17.09) previously submitted as paper in serial 0007.
November 7, 2012	0061	Study 2078 Amendment 1 of Bioanalytical report - see 0023
December 20, 2012	0062	Request for SPA - Carcinogenicity Protocol package "2-Year Oral (Gavage) Carcinogenicity Study in CD-1 (ICR) Mice. Also see 0059.
December 20, 2012	n/a - 61	Email communication to M. Scherer re: 0062 submission.
December 21, 2012	n/a - 62	SYN email response to FDA re: Dec 20th email above.
January 10, 2013	n/a - 63	Email communication to M. Scherer re: 0062 Carc SPA
January 15, 2013	n/a - 64	M. Scherer Email response to Jan 10th email above.
January 16, 2013	n/a - 65	G. Jacob email response to email above
January 22, 2013	0063	Amendment to Request for SPA - see SS0062
January 25, 2013	0064	Information Amendment - X Ref correspondence to IND115118 (SS0006)
January 30, 2013	n/a - 66	G. Jacob email to M. Scherer follow up to SPA - SS 0062 above.
January 30, 2013	n/a - 67	M. Scherer response to SPA end of review period - Feb 2, 2013
January 31, 2013	n/a - 68	FDA Exec CAC Minutes
February 8, 2013	0065	General Correspondence - Other Notification of Pending Carcinogenicity Protocol Submission for SPA (SD Rats) (also see 0068)
February 12, 2013	n/a - 69	G. Jacob Information email to FDA acknowledges CAC Minutes and revised SPA protocol; dosing to begin 2/26/13.
February 19, 2013	0066	Protocol Amendment - New Protocol SP304101-09 Food Effect Study in Healthy Adult Subjects
March 5, 2013	0067	Information Amendment - Pharm/Tox 13 Wk Oral Tox Rat
March 5, 2013	0068	Request for SPA Rat Carc 104-Wk Oral Sprague-Dawley Rats (see 0065)
March 8, 2013	n/a - 70	IND 074883 (plecanatide) - information request re: rat CARC SPA request
March 15, 2013	0069	Information Amendment - Pharm/tox Monkey study
March 15, 2013	0070	Response to FDA request Rat Carc study
March 20, 2013	0071	Protocol Amendment -New Investigator, Dr. Hernandez-Illas for Serial 0066, Food Effect Study
March 22, 2013	0072	General Correspondence - EOP2 Meeting Request CMC (x-ref IBSC)
April 11, 2013	0073	Information Amendment - Clinical Investigator's Brochure v 6.0 revision (Apr 2013).
April 12, 2013	n/a - 72	FDA Response to CARC SPA - Final CAC Report
April 15, 2013	n/a - 71	Email to FDA M. Scherer - IND 74883: Status update request re: Type B EOP2 - CMC meeting (Serial #0072)
April 16-17, 2013	n/a - 73	FDA granting EOP2 CMC meeting and SYN response and clarification.
April 30, 2013	n/a - 74	Email to FDA requesting status update on EOP2 Meeting follow-up of April 17th above.
May 1, 2013	0074	General Correspondence: Type B EOP2 CMC Meeting Pkg.
May 7, 2013	0075	General Correspondence: Type B EOP2 Clinical Meeting Pkg.
May 9, 2013	0076	Protocol Amendment: New Protocol SP304203-01 OLE study (V1)
May 20, 2013	0077	Protocol Amendment-New Investigator for CIC Study Drs. Vasudeva (471), Valor (149), Nayyar (157) and Lapham (482) previously not

		submitted.
May 22, 2013	n/a - 75	Email from Catherine Tran-Zwanetz re:IND 115118 clarification
May 22-23, 2013	n/a - 76	FDA & SYN emails re: EOP2 for CMC
May 23-24, 2013	n/a - 77	FDA & SYN emails on status of EOP2 clinical
May 27, 2013	n/a - 78	SYN letter re:clinical EOP2 authorization to TH Inc
May 28, 2013	n/a - 79	SYN email to FDA confirming the revision of the EOP2 questions that will be submitted a revised meeting request.
May 29, 2013	n/a - 80	SYN email to FDA follow-up on May 22nd email
May 30-31, 2013	n/a - 81	SYN email to FDA confirming CMC EOP2 meeting date and attendees
June 3, 2013	n/a - 82	Email to FDA of no foreign visitors to EOP2 CM
June 4, 2013	n/a - 83	FDA EOP2 CMC - Meeting Preliminary Comments
June 4, 2013	n/a - 84	M. Scherer email response to May 28th (above)" tentatively reserved July 31st for the F2F clinical meeting.
June 4, 2013	n/a - 85	SYN responses to CMC EOP2 questions from FDA
June 13, 2013	n/a - 86	SYN sent to FDA revised questions for clinical EOP2 meeting as per M. Scherer email above of June 4th.
June 18, 2013	n/a - 87.	FDA CMC Meeting Minutes
June 19, 2013	0078	Information Amendment-Pharmacology and Toxicology Final Reports SP-PH001, PH002, PH003, PH005, 06-119, 88418/070880/070973, and 88418-070888, And 88418 070888 88687 070973.
June 19, 2013	0079	General Correspondence - Dr. Griffin, CMO added to IND as CMO
June 19, 2013	0080	Information Amendment - Pharmacology and Tox Final reports 89608/080025/080092 and 91588/080627/Rev 4
June 24, 2013	n/a - 88	SYN: email F/U of FDA June 4th to confirm July 31st Mtg.
June 26, 2013	0081	Information Amendment - Final CSR Protocol 20210 (CIC)
June 26, 2013	n/a - 89	FDA Response to June 24 email confirming date of F2F Mtg.
June 26, 2013	n/a - 90	SYN Response to FDA clinical Mtg. question (SEALD)
June 27, 2013	0082	Request for Meeting - EOP2 clinical meeting package referenced in SS0075 above.
July 10, 2013	n/a - 91	SYN request for follow-up on meeting granted letter and confirmation that remaining questions will be submitted in to Matt for written response and not as a meeting request. Matt Scherer same day response included.
July 16, 2013	n/a - 92	SYN email to M. Scherer related to the SS 0083 for EOP2 mtg.
July 19, 2013	0083	Information Amendment - Pharm/Tox - Audited draft report hERG 120924.TZP.
July 26, 2013	n/a - 93	SYN & FDA communication to confirm clinical EOP2 meeting process. Request follow-up on Mtg Grant Letter.
July 30, 2013	n/a - 94	FDA Preliminary Meeting Minutes EOP2 31 July meeting
July 30, 2013	n/a - 95 95a	• SYN response to Preliminary Meeting -Based on the informative comments received from the Agency, Synergy had determined that the scheduled Type B EOP2 clinical meeting was no longer needed and this was communicated back to Matt Scherer. • SYN Internal Mtg Minutes - Not sent to FDA.
August 13, 2013	0084	Information Amendment - Pharm/Tox: 13 wk Tox in Rats
August 16, 2013	0085	Information Amendment - Pharma/Tox: Reports 0722-07246/ 0722-07281/692345/ 1275MS58.001/ 692342 and 15056
August 20, 2013	0086	Information Amendment - CMC stability
August 22, 2013	0087	Information Amendment - New Protocol SP304203-00 (CIC3) V1
August 23, 2013	0088	Information Amendment: Pharma/Tox: Final and Draft Reports 70474 and 30145. Also reference SS0085
August 30, 2013	0089	Protocol Amendment - 10 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Andrews (008), Barish (019), Blumenau (036), DuPree (098), Egelhof (103), Kaplan (203), Kirstein (217), Klein (220), Kuettel (230) and Lubin (253).

September 4, 2013	0090	Protocol Amendment - 19 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Friedenberg (469), Glover (141), Holmes (179), Horn (182), Huffman (184), Koltun (224), Krause (227), Maynard (468), Padilla (317), Patel (317), Perez (325), Schwartz (373), Sellers (376), Stamatin (473), Surowitz (408), Vasudeva (471), Wakefield (431), Wiener (435) and Wiltz (438).
September 6, 2013	0091	Annual Report 2013
September 9, 2013	0092	Protocol Amendment - 23 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Baber (14), Bargar (481), Campbell (48), Cha (54), Clark (63), Dawson (80), Ennis (106), Espinoza (365), Fogel (121), Hoekstra(178), Jasper (193), Marcadis (260), Moparty (302), Muse (302), (467), Iyer (467), Souder (395), Call (46), Gonte (148), Heurich (182), Moussa (297), Ringold (351), Singh (79), and Varunok (476).
September 12, 2013	0093	Information Amendment - Pharm/Tox Final hERG report (Final hERG from 0083) and Final Study Reports: No. 120924.TZP, No. AB20754, No. SP-PH-008, No. SP-PH-10, SP-PH-11, No. 13SYNRP1A, No. 13SYNRP1B.
September 26, 2013	0094	Protocol Amendment - 4 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Bala (16), Brown (479) DeLuca (84), and Valor (149)
October 9, 2013	0095	Protocol Amendment - Change in Protocol SP304203-00 (CIC3) V2
October 14, 2013	0096	Other - Pediatric Study Plan (PSP) (CIC/IBS-C)
November 5, 2013	0097	Protocol Amendment - 4 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Lumicao (460), McGuire (237),Naccarato (303), and Sligh (392)
November 11, 2013	0098	Protocol Amendment - Change in Protocol SP304203-01 (OLE) V2
November 14, 2013	0099	Protocol Amendment - Change in Protocol SP304203-00 (CIC3) V2.1
November 22, 2013	0100	Protocol Amendment - 5 New Investigators added to Study SP304203-00 (CIC3) Drs. Cha (54), Huffman (184), Klein (220), Koltun (224) and Surowitz (408).
November 25, 2013	n/a - 96	Email FDA M. Scherer request to separate CIC and CIBS indication for PSP. Revised submission PSP V2 - see SS0103 below.
December 3, 2013	0101	Protocol Amendment - 10 New Investigators added to Study SP304203-00 (CIC3) Drs. Andrews (008), Barish (019), Fogel (121), Glover II (141), Holmes (179), Horn (182), Krause (227), Kuettel (230), Ringold (351), and Wiener (435)
December 9, 2013	0102	Information Amendment - Final CSR Food Effect SP304101-09
December 10, 2013	0103	Pediatric Study Plan - Revised submission PSP V2
December 12, 2013	0104	Protocol Amendment - 10 New Investigators added to Study SP304203-00 (CIC3) Drs. Call (046), DuPree (098), Egelhof (103), Hoekstra (178), Jasper (193), Kaplan (203), Lubin (253), Muse (302), Naccarato(303), and Padilla (317)
December 18, 2013	0105	Information Amendment - Pharm/Tox Studies - No. 20039567, No. 20046300, No. 20035794, and No.20034218 (Plecanatide nonclinical IND of 4 pilot juvenile toxicity studies)
December 17, 2013	0106	Protocol Amendment - 10 New Investigators added to Study SP304203-00 (CIC3) Drs. Bauch (609), Doering (620), Heurich (071), Inzerello (644), Korff (641), Kroll (664), Meli Jr. (638), Sharma (657), Vargas (662), and Wiltz (438)
December 26, 2013	0107	Protocol Amendment - Change in Protocol SP304203-00 (CIC3) V2.2
January 9, 2014	0108	Protocol Amendment - 10 New Investigators added to Study SP304203-00 (CIC3) Drs. Bargar (481), Blumenau (036), Bradley (655), Deluca (084), Hilal (601), Iyer (467), Moussa (267), Perez (325), Preston (628), and Reynolds (680)
January 20, 2014	0109	Protocol Amendment - 10 New Investigators added to Study SP304203-00 (CIC3) Drs. DeLissio (700), Hubbard (617), Lindenbaum (645), McLaughlin (676), Adler (602), Lillestol (68), Muller (623), Onyema (630), Vargas (612), and Sones (685)
January 31, 2014	0110	Protocol Amendment - Change in Protocol SP304203-00 (CIC3) V3.1

January 31, 2014	0111	Protocol Amendment - 15 New Investigators added to Study SP304203-00 (CIC3) Drs. Dawson (80), Cova (699) Wombolt (652), Clark (63), Klein (636), Espinoza (355), Goldstein (637), DeSantis (618), Valor (149), Pucillo (77), Desta (613), Brandon (696), Florez (684), Schilling (654), and Dulitz (632).
February 11, 2014	0112	Protocol Amendment - 35 New Investigators added to Study SP304203-00 (CIC3) Drs. Funk (616), Whitmer (694), Holbrook (672), Ricci (619), Friedenberg (469), Bhandari (639), Kaplan (675), Bruce (643), Farsad (689), Khan (663), Farris, (702), Silvers (633), Maletz (671), Andersen (640), Estevez (605), Sutter (687), Mariano (653), Rashbaum (678), Keller (661), Aguilar (607), Barton (693), Samson (600), Tarleton (604), Matusow (688), Mullen (708), Rock (648), Qadri (649), Herrington (660), Hunter (624), Springsteen (692), Baber (14), Tatu (658), Singh(674), Geisberg (634), and Webster (606).
February 25, 2014	0113	Protocol Amendment - 20 New Investigators added to Study SP304203-00 (CIC3) Drs. Erwin (603), Kim (706), Dawood (615), Carter (730), DeBusk (656), Serfer (667), Malik (629), Rausher (716), Nicholson-Uhl (626), Kessler (695), Yazdi (621), Badar (709), Chachar (608), Berman (647), Sensenbrenner (686), Cifuentes (719), Suarez (631), Wagner (627), Vaughn (705), and Mikhail (625).
March 3, 20114	0114	Information Amendment - New Protocol SP304203-03 Global V1 (NCIC3)
March 14, 2014	n/a - 97	FDA Advice Information Request Response to iPSP submission letter
March 17, 2014	0115	Protocol Amendment - 15 New Investigators added to Study SP304203-00 (CIC3) Drs. Oguchi, (697), Al-Amin (736), Bohman (665), Karimjee (735), De La Portilla (718), Wingo (635), Azzam (683), Chhablani (691), Rigby (650), Souder (395), Marilley (701), Lesh (724), Hardi (734), Clark (651), and Nalamachu (614).
March 17-19, 2014	n/a - 98	Emails re omission of V3 0 CIC3 protocol to IND
March 24, 2014	0116	Protocol Amendment - Change in Protocol SP304203-00 (SOC V3.0 & V3.1)
March 25, 2014	0117	Protocol Amendment - 3 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Dimitroff (089), Liakos, Dorn (920), and Oberoi (311). + (12) Revised Form 1572
March 31, 2014	0118	Information Amendment - Change in Protocol SP304203-03 National V2.1 (NCIC3)
April 7, 2014	0119	Pediatric Study Plan PSP V3 revised in response to FDA inquiry of March 14, 2014 (n/a-97) above.
April 14, 2014	0120	Information Amendment - CMC updates to drug substance process.
April 22-24, 2014	n/a - 99	Email Communications from FDA and SYN response to PSP submission of SS 0119 above.
April 28, 2014	0121	Protocol Amendment - 8 New Investigators added to Study SP304203-03 (CIC3National) Drs. Schmidt (328), Earl (329), Feldman (333), Sotolongo (334), Young (335), Gershenbaum (383), Berenguer (397) & Gonzalez (455) + Drug label
April 29, 2014	n/a - 100	SYN email to FDA M. Brancazio Revised Pediatric Study Plan (PSP) V4
April 29, 2014	0122	Pediatric Study Plan (PSP) V4
May 06, 2014	0123	Protocol Amendment - 7 New Investigators added to Study SP304203- 01 (OLE CIC3) Drs. Florez (684), Hubbard (617), Schilling (654), Vargas (662), Meli (638), Onyema (630) & Goldstein (637). 15 New Investigators added to Study SP304203-00 (CIC3) Drs. Florea (611),Willette (642), Triebling (682), Ginsberg (703), Kuliev (710), Daboul (711), Poonawala (712), Guss (707), Arif (738), Gonte (148), Miner (646), Bacha (713), Campbell (742), Lucksinger (741) & Sligh (392) + (3) Revised Form 1572

May 15, 2014	0124	Information Amendment -Nonclinical Final Report Study No. 20049883 (GLP-compliant dose range-finding study in juvenile mice) and draft Protocol Study No. 20059246 (Juvenile toxicity study in mice)
May 16, 2014	0125	Response To FDA Request For Information - TQT
May 21, 2014	n/a -101	FDA request of Clin Pharm Cardiac Safety related to TQT Waiver
May 22, 2014	0126	General Correspondence - Sponsor Change of Address
May 27, 2014	0127	Protocol Amendment - 11 New Investigators added to Study SP304203-00 (CIC3) USA Drs. Pruitt (714), Patton (723), Zakko (729), Tagore (717) ; Canada Drs. Green (720), Lasko (679), Pliamm (668), Aggarwal (7250, Gagné (673), Fraser (690), & Schacter (722) 7 New Investigators added to Study SP304203- 01 (OLE CIC3) Drs. Liakos (463), Preston (628), Stephen Funk (616), Ricci (619), Korff (641), De La Portilla (718), and Adler (602). 35 New Investigators added to Study SP304203-03 (National CIC3) Drs. Prida (261), Chalhoub (269) ,Lentz (2910,Lasala (307), Trevino (322), Downing (3230, Swor (324), Powell (326), Fowler (330), Layle (337), Wolfson (357), Guerra (363), Ocampo(366), Scheeler (367), Rubino (375), Maiquez (379), Dever (384), Barbel-Johnson (393), Fidelholtz (394), Jarrett (399), Schreiber (401), Lustbader (409), Deck (411), Maldonaldo (415), Finneran (423), Tamayo (424), Sanchez (428), Intelisano (429), Manning (451), Dinh (459), Cheekati (465), Nguyen (478), VanDermark (485), Homoky (493), & Aplizar (495).
June 5, 2014	0128	Protocol Amendment - 4 New Investigators added to Study SP304203-00 (CIC3) USA Drs. Parmar (728), Rao (727) & Dorn (092) and Canada Dr. Lee (698) +Revised 1572 Dr. Mullen. 7 New Investigators added to Study SP304203- 01 (OLE CIC3) Drs. Nicholson-Uhl (626), Whitmer (694), Singh(674), Vaughn (705), Wagner (627), Aguilar (607) & Kaplan (675) 33 New Investigators added to Study SP304203-03 (National CIC3) Drs. Acosta (234), Ledo-Sanchez (235), Garcia (240), Pouzar (241), Kalafer (243), Christina (255), Hadi (257(, Vora (262), Usdan (268), Saumell (272), Alvarez (273), Hazan (282), Braun (284), Ramos (285), Kalen (312), Kravitz (340), Fox (243), Steinberg (344), Khan (345), Jayson (348), Hudson (350), Ruiz (354), McGuire (356), Khan (371), Bretton (382), Jessani (396), Champlin (400), Marquez (402), Blatt (407),Terrelonge (414), Hyett (417), Gonzalez (419) & Grant (425).
June 6, 2014	0129	Response To FDA Request For Information - TQT Follow-up
June 16, 2014	0130	Information Amendment: Nonclinical Study Reports Study No.AB23825 (To evaluate, in Radioligand Binding, and Tissue assays), Study No.13SYNRP2 (Assessment of the Stability of Plecanatide in Surgically Ligated Rat Intestinal Loops) and Study No. 20046300 (Study Report Amendment Plecanatide: An Acute Oral Toxicity Study in Pre-weanling and Weanling CD-1 Mice (Final Summary Report Amendment No.1)
June 18, 2014	0131	Protocol Amendment - 3 New Investigators added to Study SP304203-00 (CIC3) USA Drs. Vagujhelyi (622); Canada Drs. Rheault (610),and Blouin (739). 9 New Investigators added to Study SP304203- 01 (OLE CIC3) Drs. Lillestol (681), Bhandari (639), Suarez (631), Estevez (605), Francyk (609), Bradley (655), Marilley (701), Rigby (650), and Barton (693). 42 New Investigators added to Study SP304203-03 (National CIC3) Drs. Weinstein (242), Mbogua (247),Blanco (276), Izquierdo (279), Clarke (280), Roche (281), Fernandez (283), Race (287), Fisher Jr.(227), Winder (267), Bloom (278), Bassan (288), DeMicco (299), Holt (308), Soucie (358), Kim (361), Nand (362), Gross (387), Goldstein

		(404), Parrillo (406), Edris (422), Goetsch (427), DaCosta (457), Radin (482), Dawson (492), Berg (496), Davidson (430), Waldbaum (432), Vo (433), Ackerman (436), Moya (448), Poss (452), Brinson (464), Lorch Jr.(480), Kashyap (484), Iyer (487), Bravo (488), Saway (489), Stewart (494), Gothard (497), Akins (498), and Labissiere (499)
June 18, 2014	n/a - 102	FDA Advice letter SP-304 plecanatide on Juvenile Toxicology
June 25, 2014	0132	Annual Report 2014
July 9, 2014	0133	**Protocol Amendment - 1 New Investigators added to Study SP304203-00 (CIC3) USA Dr. Wolosin (732)** **10 New Investigators added to Study SP304203- 01 (OLE CIC3) Drs.** Farsad (689), Geisberg (634), Klein (636), Mullen (708), Sutter (687), McLaughlin (667), Pucillo (677), Rausher (716), Kessler (695), and Qadri (649). **45 New Investigators added to Study SP304203-03 (National CIC3)** Bellingar (440), Mahmud (206), Seiden (208), Soefje (211), Wolfrum (212), Schoffner (216), Gutierrez-Stone (219), Miranda (221), Walland (226), Frei (228), Herring (230), Ingham (277), Vento (289), Harris (298), Boghara (301), Moretti (304), Crespo (306), Provenza (318), Randall (338), Corder (320), Gimness (327), Banks (339), Elder (389), Woyshville (931), Ayub (403), Echarri (445), Willits (446), Mock (353), Chaykin (474), Maw (477), Arroyo (483), White (486), Shoemaker (205), Fitzgerald (207), Mehta (209), Kirby (229), DeGarmo (252), Columbi (231), Kellogg (236), Trueba (239), Hewitt (244), Abbas (246), Raoof (248), Davis (253), & Vaz (256)
August 6, 2014	0134	Information Amendment - CMC drug substance and drug product sections updates & SYN f/u to CMC EOP2 (7 Jun 13) response to question 7
August 7, 2014	n/a - 103	FDA email Advise/Information for TQT Waiver Request
August 12, 2014	0135	**Protocol Amendment - 1 New Investigators added to Study SP304203-00 (CIC3) Dr. Garcia (745).** **24 New Investigators added to Study SP304203- 01 (OLE CIC3) Drs.** Kroll (664), Carter (730), Cifuentes (719), Mikhail (625), Dulitz (632), Desta (613), Berman (647), Farris (702), DeBusk (656), Morris (612), DeLissio (700), Serfer (667), Sharma (657), Ginsberg (703), Mariano (653), Silvers (633), Al-Amin (736), Tarleton (604), Kim (706), Wombolt (652), Sensenbrenner (686), Daboul (711), Karimjee (735), & Muller (623). **9 New Investigators added to Study SP304203-03 (National CIC3)** Drs. Cohen (213), Zeno (265), Guerrero (275), Jimenez-Barredo (290), Snoy (294), Dao (447), Madoff (257), Penate (415), & Morgan (279).
August 15, 2014	0136	Response to FDA Advice Letter SP-304 Plecanatide on Juvenile Toxicity Studies (20059246 Plecanatide Protocol & 20059246 Plecanatide Protocol Amendmen).
September 9, 2014	0137	Information Amendment - Clinical Investigator's Brochure v 7.0 revision (Aug 2014).
September 18, 2014	0138	Information Amendment - CSR Amendment 1 Protocol 20210 (CIC)
September 22, 2014	0139	**Protocol Amendment - 11 New Investigators added to Study SP304203-00 (CIC3) USA** Drs. Prieto (355), Ojuri (740), Lane (750), Deshmukh (744), Watson (752), Rigolosi (751), Yeoman (753), Simmons (756), Lacy (721), and Canada Dr. Campbell (743), Godsell (746). **15 New Investigators added to Study SP304203- 01 (OLE CIC3)** Drs. Bansal (373), James (640), Chhablani (691), Keller (053), Miner, Jr. (646), Hardi (734), Hunter (624), Azzam (683), Lesh (724), Bohman (665), Rock (648), Campbell (742), Willette (642), Badar III (090), and Lindenbaum (645).

October 14, 2014	0140	Information Amendment - CMC drug substance and drug product sections updates (SS 0134)
October 20, 2014	n/a - 104	FDA response SYN email request for FU on PSP (SS0122 above)
November 10, 2014	0141	Information Amendment (Pharma/Tox) - Follow-up (SS 0062 above)
November 18, 2014	n/a - 105	FDA response to SS0141 Follow-up to SPA CARC
Nov 18 & 21, 2014	n/a - 106	Email communication with FDA M. Brancazio requesting following up on PSP (SS 0122) and his response.
November 25, 2014	0142	Protocol Amendment - 6 New Investigators added to Study SP304203-00 (CIC3). Drs. Goldstein (748), Karyotakis (749), Soufer (757), DiGiovanna (758), MacGillivray (763), and Pruthi, (674) - 14 New Investigators added to Study SP304203- 01 (OL CIC3) USA Drs. Samson (600), Chachar (608), Clark (651), Khan (663), Pruthi (674), Reynolds (680), Oguchi (697), Parmar (728), Zakko (729), and Lucksinger (741) Canada Drs. Pliamm (688), Fraser (690) ,and Blouin (739) - 19 New Investigators added to Study SP304203-03 (National CIC3) Drs. Ampajwala (497), Anandu (198), Binker (266) DeLa Llana (237) Joseph (368), Latorre (364),Lefebvre (349), Toler Meyers (385), Ortiz (210), Polster (372), Protell (201), Sanabria (445), Seco (360), Slandzicki (429), Tement (342), Van (359), Vega (195), Wilhoit (365), Volpe (279) Revised Transfer of Obligation CIC3 &OL)
December 3, 2014	n/a - 107	SYN EMAIL to FDA for follow-up on SS 0141 SPA for Mouse Carcinogenicity Study
December 4, 2014	n/a - 108	FDA Response to SS0141 SPA CARC
December 5, 2014	n/a - 109	FDA Response to Revised Pediatric SP v4 (SS 0122 above)
December 5, 2014	0143	Protocol Amendment - change in protocol SP304203-01 (OLE now LTS) Version 3.0
December 29, 2014	0144	Protocol Amendment - change in protocol SP304203-01 (OLE now LTS) Version 4.0
December 29, 2014	0145	Information Amendment Response to FDA Advice/Revised PSP v5 (SS 0122 above)
December 29, 2014	0146	Information Amendment (Pharma/Tox) - Follow-up to SPA CARC (SS 0068 above)
December 31, 2014	0147	General Correspondence - Change in Synergy Authorization signature to EJaeger.
January 16, 2015	n/a - 110	SYN EMAIL to FDA Plecanatide Rat CARC Study SS 0146
January 16, 2015	0148	Protocol Amendment -11 New Investigators added to Study SP304203- 01 (OLE CIC3) USA Drs. Clarence (622), Dotherow (685), Yazdi (621), Lane (750), Rigolosi (751), Kuliev (710), Gordon (672), and Arif (738) Canada Drs.Toma (679), Lee (698), and Rheault (610) - 1 New Investigators added to Study SP304203-03 (National CIC3) Dr. Eugene (499).
Jan 22, 2015	n/a - 111	Email from FDA to IND 74883 Serial 0146 (plecanatide rat carcinogenicity study)
January 30, 2015	0149	Request For Proprietary Name Review
February 2, 2015	0150	Information Amendment (Pharma/Tox) - Follow-up to Rat CARC Study (SS 0146 above)
February 3, 2015	n/a - 112	Email FDA SYN follow up on SS 0150 rat carcinogenicity study
February 4, 2015	n/a - 113	Email to FDA to confirm Agreed Upon Pediatric Study Plan submission
February 6, 2015	n/a - 114	EMAIL SYN TO FDA as follow-up Final Agreed Upon PSP (V5) SS0151
February 6, 2015	0151	Response to FDA Request for Information - Agreed Upon iPSP (V5)
February 9, 2015	0152	Request For Proprietary Name Revised
February 10, 2015	n/a - 115	Email to FDA request for WORD iPSP SS# 0151
February 12, 2015	0153	Protocol Amendment -12 New Investigators added to Study SP304203-

		00 (CIC3) Drs. Goisse (191), Focil (196), Erman (197), Levy (200), Jacobs (223), Lentnek (483), Llerena (295), Ruderman (204), Slye (484), Taber (319), Torres (482), and Drummond (245) - 2 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Yeoman (753) and Brandon (696).
February 23, 2015	0154	Information Amendment - Nonclinical Studies (Pharma/Tox) previously submitted on paper (11 Final Reports: SP-PH-004, VMF00019, VMF00007, 018683, 30169, 30155, VMF00009, VMF00028, 0020001133, VMF00029, & 20003036
March 5, 2015	0155	IND Safety Report Initial MFR Report no. US-000031, 1571, MedWatch Report
March 6, 2015	0156	Protocol Amendment - OL Change in Protocol & Revised Label
March 23, 2015	n/a - 116	FDA Advice - Pediatric Study Plan notification
April 15, 2015	0157	Protocol Amendment - Change in Protocol SP304203-00 (CIC3) V4.0
April 27, 2015	n/a - 117	Plecanatide INDs 74883 and 115118 - CMC information follow-up request
May 1, 2015	0158	Information Amendment - Bioanalytical validation reports for the measurement of SP-304 and SP-338 in plasma from various species. Reports 1988, 2474, 2475, 2142, 1991, 2452, 2066, 2492, 2486 2067, 2476, 2431, and 2432
May 4, 2015	0159	**Protocol Amendment -7 New Investigators added to Study SP304203- 00 (CIC3)** Drs. Agarwal (755), Francyk (609), Gordon (672), Dotherow (685), Caves (622), Chiong (295), and Toma (679). **5 New Investigators added to Study SP304203-01 (OLE CIC3)** Drs. Agarwal (755), Simmons (756), Soufer (757), Prieto (355), and Tatu (473)
May 5, 2015	0160	Information Amendment - Change in Protocol SP304203-03 National Version 3.0 (NCIC3)
May 5, 2015	0161	Protocol Amendment - Change in Protocol SP304203-01 (OLE now LTS) Version 5.0
May 11, 2015	0162	General Correspondence - CMC following Synergy's IBS-C EOP 2 meeting for IND 115118 & associated with IND 74883 Synergy proposed to submit at least one batch of drug substance and drug product manufactured using S-acetamidomethyl-L-cysteinyl
May 28, 2015	0163	Type B Pre-NDA Clinical and CMC Meeting Request
May 29, 2015	n/a - 118	FDA Email re Pre-IND mtg request SS0163 separate clin & CMC
June 3, 2015	0164	Type B Pre-NDA Clinical/Nonclinical Request for Meeting
June 5, 2015	0165	Information Amendment - CMC Chemistry Manufacturing, and Control
June 10, 2015	0166	Protocol Amendment -3 New Investigators added to Study SP304203-00 (CIC3) Drs. Latortue (752), Pulicharam (687), and Stone (724). 5 New Investigators added to Study SP304203-01 (OLE CIC3) Drs. Morin (182), Stone (724), Campbell (746), Godsell (746), and Gagne (673).
June 10, 2015	0167	Information Amendment - Statistics (V 1.0, dated 02 June 2015) Protocol SP304203-00
June 15, 2015	0168	Information Amendment - Pharmacology/Toxicology reports - final reports /amendments for studies of primary pharmacology, pharmacokinetic, analytical methods, and metabolism - (13 Reports SP-PH-010, SP-PH-016, 06-169, 100006614,VMF00002DX,1896-003, 1896-010, 20043655,1896-004, 0020002293,1896-019,1896-020 and, SP-PH-015
Jun 17, 2015	n/a - 119	SYN email to FDA requesting FU of preNDA Mtg Request

June 18, 2015	n/a - 120	IND 74883 CMC Meeting Request Granted letter
June 19, 2015	n/a - 121	SYN email acknowledgment of CMC Meeting Request Granted
June 23, 2015	n/a - 122	SYN email to FDA FU on Clinical Mtg Request
June 23, 2015	n/a - 123	FDA email Clinical Pre-NDA meeting granted letter
June 23, 2015	n/a - 124	SYN email to FDA acknowledge clinical_noncliin type B meeting request granted
Jun 25, 2015	n/a - 125	SYN email to FDA Type C mtg clarification
June 26, 2015	0169	Protocol Amendment -1 New Investigator added to Study SP304203- 03 (NCIC3) Dr. Nualart + 1572 Updates
June 26, 2015	0170	Information Amendment - Statistics (V 1.0, dated 02 June 2015) Protocol SP304203-03

June 30, 2015	0171	General Correspondence - Pre-NDA CMC Meeting Briefing Package
June 25, 2015	n/a - 126	FDA Proprietary Name Unacceptable
July 1, 2015	n/a - 127	SYN email to FDA Clinical type B meeting request granted
July 6, 2015	n/a - 128	SYN email to FDA Clinical type B Mtg granted related email
July 7, 2015	0172	General Correspondence - Pre-NDA Clinical/Nonclinical Meeting Briefing Package
July 16, 2015	0173	Information Amendments - Pharmacology/Toxicology and Clinical Pharmacology (8 final/amendment Reports SP-PH-001, SP-PH-002, SP-PH-003, 14SYNRP2R3-B, 0066-13, 0066-13-01, RSN00008, and SP-PH-018)
July 21, 2015	n/a - 129	Email to FDA re CMC F2F Mtg Request FU
July 24, 2015	n/a - 131	CMC Meeting Preliminary Comments
July 27, 2015	n/a - 132	EMAIL to FDA of SYN response to CMC Preliminary Mtg Comments
July 27, 2015	n/a - 132a	SYN email Preliminary Meeting Comments
July 27, 2015	n/a - 133	Final IND 74883_Synergy Reponses to Preliminary Mtg Response 27JUL2015 CMC
July 27-28, 2015	n/a - 134	Email FDA for listing of CMC attendees for PreNDA Mtg
July 29, 2015	n/a - 135	Email to FDA List of SYN Clin attendees and FU prell mtg comments
July 30, 2015	n/a - 136	Email to FDA of TopLine NCIC3 results
July 30, 2015	n/a - 136a	FDA acknowledgement of Topline tables
Aug 2, 2015	n/a - 137	FDA IND 74883 Plecanatide Lobbyguard
Aug 4, 2015	n/a - 138	FDA EMAIL with Clinical Plecanatide Preliminary Comments 7-20-15
Aug 4-5, 2015	n/a - 139	SYN EMAIL acknowledging Clinl Preliminary Mtg Comments
Aug 4, 2015	0174	Information Amendment - Pharmacology/Toxicology (3 final/amendment Reports SP-PH-004, 20053292, and 20059246)
Aug 5, 2015	n/a - 140	SYN response to Clin Preliminary Mtg Comments
Aug 5, 2015	n/a - 140a	SYN acknowledge Clinical Preliminary Comments
Aug 5, 2015	n/a - 140b	FDA Email Response on FDA Staff present for the Preliminary mtg.
Aug 11, 2015	n/a - 141	CMC IND 74883 7-28-2015 CMC Meeting Minutes
Aug 19, 2015	n/a - 142	Email to FDA to n/a140a above including requested information to Questions 5 and 7.
Aug 31, 2015	n/a - 143	EMAIL Response to FDA Exposure query
Sep 1-2, 2015	n/a - 144	Email from FDA - confirmation receipt of the response to FDA Exposure query (IND 74883 Plecanatide-Synergy Information Request 9-1-201)
Sep 3, 2015	0175	Protocol Amendment - Change in Protocol SP304203-01 (OLE now LTS) Version 6.0
Sep 14, 2015	n/a - 145	Email to FDA on status Prel Mtg Min and Blue Stream Validation Rpt
Sep 15, 2015	0176	Annual Report 2015
Sep 21-22, 2015	n/a - 146	Clinical preNDA Meeting Minutes
Sept 23, 2015	n/a -147	FDA email response preNDA Clinical Mtg Minutes
Sept 24, 2015	n/a - 148	FDA pre-assigned NDA number
Oct 8, 2015	n/a - 149	SYN request for follow_up on 141 above
Oct 21, 2015	n/a - 150	SYN request for follow-up above 146
Oct 21, 2015	0177	Information Amendment - Pharmacology/Toxicology and Clinical Pharmacology (7 final/amendment Reports SP-PH-001,13SYNRP2R1, 14SYNRP2R3_A, 20053292, 20059246, 13SYNRP6A & 13SYNRP6B)
Oct 27, 2015	0178	Protocol Amendment -68 New Investigators added to Study SP304203-01 (OL) Drs. Acosta (234), Alpizar (495), Alvarez (273), Berenguer (397), Berg (496), Binker (266), Bravo (488), Cardona (402), Cheekati (465), Dever (384), Dinh (459), Duardo-Guerra (363), Dushkin (340), Edris (422), Eugene (499), Fisher, Jr. (227), Freed (407),Goldstein

		(404), B. Gonzalez (455), J. Gonzalez (419) , Grant (425), Gutierrez-Stone (219) , Herring, Jr. (230), Layle (337), Ledo-Sanchez (235), Lefebvre (349), Lentz (291), Lustbader (409) , Mahmud (206), McGuire (356),Nand (362), Nualart (231), Ocampo (366), Penate (415), Prida (261) ,Ramos (285), Saumell (272), Scheeler (367), Slandzicki (429) ,Soucie (358), Tamayo (424) , Trevino (322), Trueba (239),Usdan (268) , Varela (414),Velazquez (483), Vora (262), Willits (446) ,Wolfson (357), Young (335), Akins (498) ,Blanco (276) ,Feldman (333) , Fernandez (283), Fidelholtz (394), Fox (343), Frias (275), Douglas (350), Latorre (364), Lorch, Jr. (480), Miranda (221), Moya (448) ,Petersen (396), Ruiz (354), Sanabria (445), Sanchez (428), Seco (360), and Vento (289) + TOO CIC3, OL & NCIC3
November 5-6, 2015	n/a - 151	Email to FDA - Pediatric Study Protocol status request
November 17, 2015	0179	Request For Proprietary Name Review Primary Name: Trulance (Plecanatide)
December 3, 2015	0180	Protocol Amendment -2 New Investigators added to Study SP304203-01 (OL) Drs. Khan (345) and Vega (195); + Revised 1572 Dr. Rao
December 4, 2015	0181	Information Amendment - Final CSR CIC3 SP304203-00
December 8, 2015	0182	Information Amendment - Pharmacology/Toxicology (4 Final Reports SP-PH-019, SP-PH-020, 12-2324, & 1896-011)
December 11, 2015	0183	Protocol Amendment -1 New Investigator 1572 Update to Study SP304203-03 (NCIC3) Dr. Vega (195)
December 14, 2015	0184	Information Amendment - Final CSR CIC3 SP304203-03
December 18, 2015	0185	Information Amendment -FDA Mtg minutes drug stability Question 4
December 22, 2015	0186	Information Amendment - Pharmacology/Toxicology (5 Final Reports SYN-GJ-080108C, SYN-GJ-080108M, 1896-021,1896-022 and SYN-GJ_080616C)
December 28, 2015	n/a - 152	Email to FDA - final draft pediatric study protocol SP304202-13
December 28, 2015	0187	Information Amendment - CSR Protocol SP304203-00 & 03; Section 14.3.3, Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
December 31, 2015	0188	Protocol Amendment - Pediatric New Protocol SP304202-13 (Draft Version 1.0)
January 12, 2016	0189	Information Amend - Pharmacology/Toxicology (1 Final Report No.1896-023)
January 18, 2016	0190	Response to FDA Request for Information - Blue Stream Validation Rpt TR15-0283
January 20, 2016	n/a - 153	Email communication on Synergy User Fee Waiver Documentation - Status Request
January 20, 2016	n/a 153a	FDA letter on the User Fee Waiver Granted - Synergy
January 26, 2016	0191	Information Amendment - Clinical Investigator's Brochure v 8.0 revision (Jan 2016).
Feb 11, 2016	n/a - 154	Email from FDA -NDA Information Request 1.11.16 on the summary site level data
Feb 11, 2016	n/a - 155	Email from FDA - NDA 208745 Plecanatide-Synergy Acknowledgement
Feb 22-23, 2016	n/a - 156	Email from FDA - status update on Pediatric Study PSP
Feb 23, 2016	n/a - 157	Email to FDA Cross Ref to IND 74883 request Proprietary Name Review
March 7, 2016	0192	Information Amendment - Statistics (V 2.0, dated 26 Feb 2016) Protocol SP304203-01
April 12, 2016	0193	Response to FDA Request for Information - Blue Stream Validation Rpt
April 19, 2016	0194	Information Amendment - Pharma/Toxicology (1 Final Report No.1896-024)▫
May 3, 2016	0195	Information Amendment - Protocol SP304203-00, CSR Amendment 1 (dated April 28, 2016)
May 3, 2016	0196	Information Amendment - Protocol SP304203-03, CSR Amendment 1 (dated April 28, 2016)

May 16, 2016	n/a - 158	SYN follow up on status of the request for proprietary name review for Trulance
May 20, 2016	0197	Protocol Amendment -3 New Investigators added to Study SP304203-01 (OL) Drs. Klymiuk (054), Chang (396), and Terrelonge (414) + Revised 1572 Dr. Berman.
May 25, 2016	0198	Information Amendment - Final CSR SP304203-01 (OL)
June 20, 2016	0199	Information Amendment - Pharma/Toxicology Study (3 Report Amendments 2475, 2486, 12-2324)

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Original (Exploratory) Pre-IND Meeting Request Letter was sent to:
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Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266
301-796-1008 (Brian)

Original (Exploratory) and Traditional Pre-IND Meeting Request Letters and Meeting Information Package were addressed to:
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Room RM5112
Silver Spring MD 20993
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Fax 301-796-9905 or 301-796-9895
E-mail brian1.harvey@fda.hhs.gov

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Division of Gastroenterology Drug Products
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Phone: 301-796-2120 (division secretary)
Fax: 301-796-9905
E-mail: kristen.everett@fda.hhs.gov

Pre-IND Meeting Submission Package was sent to:
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UNITED STATES PATENT AND TRADEMARK OFFICE

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Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

MAR - 7 2017

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 7,041,786 was filed on February 7, 2017, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application Trulance™ (plecanatide), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Ivor R. Elrifi
Cooley LLP
1114 Avenue of the Americas
New York, NY 10036

U.S. FOOD & DRUG
ADMINISTRATION

SEP 2 0 2017

Re: TRULANCE
Patent No. 7,041,786
Docket No. FDA-2017-E-4282

Acting Director
United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director:

This is concerning the application for patent term extension for U.S. Patent No. 7,041,786 filed by Synergy Pharmaceuticals, Inc., under 35 U.S.C. 156. The human drug product claimed by the patent is TRULANCE (plecanatide), which was assigned new drug application (NDA) No. 208745.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. 156(f)(1).

The NDA was approved on January 19, 2017, which makes the submission of the patent term extension application on February 7, 2017, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002
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cc: Ivor R. Elrifi, Esq.
Cooley LLP
1114 Avenue of the Americas
New York, NY 10036

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

JUL 18 2018

Attention: Beverly Friedman

Dear Sir:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 7,041,786. The application was filed on February 7, 2017, under 35 U.S.C. § 156.

The patent claims a product which has been subject to review under the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Tal
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Ivor R. Elrifi
Cooley LLP
1114 Avenue of the Americas
New York, NY 10036

RE: TRULANCE® (plecanatide)
Docket No. FDA-2017-E-4282

FDA U.S. FOOD & DRUG ADMINISTRATION

Re: TRULANCE
Patent No.: 7,041,786
Docket No.: FDA-2017-E-4282

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

NOV 19 2018

Dear Acting Director:

This is in regard to the application for patent term extension for U.S. Patent No. 7,041,786, filed by Synergy Pharmaceuticals, Inc., under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for TRULANCE (plecanatide), the human drug product claimed by the patent.

The total length of the regulatory review period for TRULANCE is 3,186 days. Of this time, 2,829 days occurred during the testing phase and 357 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: May 2, 2008.

   FDA has verified the Synergy Pharmaceuticals, Inc. claim that May 2, 2008, is the date the investigational new drug application (IND) became effective.

2. The date the application was initially submitted with respect to the new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act: January 29, 2016.

   FDA has verified the applicant's claim that the new drug application (NDA) for TRULANCE (NDA 208745) was submitted on January 29, 2016.

3. The date the application was approved: January 19, 2017.

   FDA has verified the applicant's claim that NDA 208745 was approved on January 19, 2017.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
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This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Ivor R. Elrifi, Esq.
Cooley LLP
1114 Avenue of the Americas
New York, NY 10036

Re: TRULANCE
Patent No. 7,041,786
Docket No. FDA-2017-E-4282

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

AUG 0 5 2019

Dear Director Iancu:

This is in regard to the patent term extension application for U.S. Patent No. 7,041,786 filed by Synergy Pharmaceuticals, Inc. under 35 U.S.C. § 156. The patent claims TRULANCE (plecanatide), a human drug product reviewed in new drug application (NDA) 208745.

In the December 4, 2018, issue of the Federal Register (83 Fed. Reg. 62590), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before June 3, 2019, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6250
Silver Spring, MD 20993
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cc: Ivor R. Elrifi, Esq.
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PTO/SB/81A (12-08)
Approved for use through 03/31/2011. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,041,786
Issue Date	May 9, 2006
First Named Inventor	Kunwar Shailubhai
Title	GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS
Attorney Docket No.	376464-2000US1(00008)

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

162421

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right.

OR

☐ Firm or Individual Name	
Address	
City	State / Zip
Country	
Telephone	Email

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature		Date	August 22, 2019
Name	Robert Goodman	Telephone	
Title and Company	VP and Associate General Counsel, IP, Bausch Health Ireland Limited		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☐ A total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	39116327
Application Number:	10107814
International Application Number:	
Confirmation Number:	9117
Title of Invention:	GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS
First Named Inventor/Applicant Name:	Kunwar Shailubhai
Customer Number:	58249
Filer:	Domingos J. Silva/Katie Wray
Filer Authorized By:	Domingos J. Silva
Attorney Docket Number:	SYPA-001/01US 321994-2051
Receipt Date:	09-APR-2020
Filing Date:	28-MAR-2002
Time Stamp:	17:14:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73	376464-2000US1-Assignee-Statement.pdf	313181 e366cc5a1c5d1eb5c8f370f247d32e561fe999e7	no	13

Warnings:

Information:					
2	Power of Attorney	376464-2000US1-Bausch-Health-Executed-POA.pdf	222465 b5ee88a043df248908c1fd7263d581bbe8691d75	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	535646	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/96 (11-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Bausch Health Ireland Limited

Application No./Patent No.: 7,041,786 Filed/Issue Date: May 9, 2006

Titled: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAM

Bausch Health Ireland Limited, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel_____, Frame_____, or a copy* is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Kunwar Shailubhai; Gregory Nikiforovich; Gary S. Jacob To: SYNERGY PHARMACEUTICALS INC.

The document was recorded in the United States Patent and Trademark Office at
Reel 021031, Frame 0438, or a copy* is attached.

2. From: SYNERGY PHARMACEUTICALS INC. To: Bausch Health Ireland Limited

The document was recorded in the United States Patent and Trademark Office at
Reel_____, Frame_____, or a copy* is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel_____, Frame_____, or a copy* is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ *As required by 37 CFR 3.73(b)(1)(i), if a copy/copies is/are attached, the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Domingos J. Silva/ April 9, 2020
Signature Date

Domingos J. Silva, Ph.D., J.D. 64197
Printed or Typed Name Title or Registration Number

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT ASSIGNMENT AGREEMENT – UNITED STATES

THIS PATENT PROPERTY ASSIGNMENT AGREEMENT – UNITED STATES, dated as of March 6, 2019 (this "Agreement"), is made by and among Bausch Health Ireland Limited, a private limited company organized under the laws of Ireland (the "Assignee"), and Synergy Pharmaceuticals Inc., a Delaware corporation (the "Parent"), and its wholly-owned subsidiary, Synergy Advanced Pharmaceuticals, Inc., a Delaware corporation ("SF Sub") (each of the Parent and SF Sub, an "Assignor" and collectively, the "Assignors"). Each of the Assignee and the Assignors are referred to individually herein as a "Party" and collectively as the "Parties." Capitalized terms used herein and not otherwise defined shall have the respective meanings set forth in the Asset Purchase Agreement (as defined below).

RECITALS:

WHEREAS, the Assignee and the Assignors have entered into that certain Asset Purchase Agreement, dated as of December 11, 2018, as amended and restated on January 4, 2019 (as further amended, restated, supplemented or otherwise modified from time to time, the "Asset Purchase Agreement"); and

WHEREAS, this Agreement is made and delivered pursuant to the terms and subject to the conditions set forth in the Asset Purchase Agreement.

AGREEMENT:

NOW, THEREFORE, subject to the terms and conditions of the Asset Purchase Agreement, and in consideration of the representations, warranties, covenants and agreements set forth therein, the Parties hereto agree as follows:

1. Acquired Patents. For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Assignors hereby irrevocably and unconditionally sell, transfer, assign, convey, and deliver to the Assignee and its successors and permitted assigns, forever, and the Assignee accepts and acquires from the Assignors all of the Assignors' right, title, and interest (of every nature, kind, and description, tangible or intangible (including goodwill), whether real, personal, or mixed, whether accrued, contingent, or otherwise, wherever located), in each case free and clear of any and all Encumbrances (other than Permitted Post-Closing Encumbrances) in, to, and under all of Seller's right, title and interest in and to those patents and patent applications set forth on Schedule I hereto (the "Acquired Patents"), including (i) all of Assignors' rights in and to all income, royalties, damages and payments now or hereafter due or payable with respect thereto, (ii) all causes of action (whether in law or in equity) with respect thereto, and (iii) the right to sue, counterclaim, and recover for past, present and future infringement of the Acquired Patents.

2. Further Assurances. This Agreement has been executed and delivered by the Assignors with the agreement that the same may be recorded with the United States Patent and Trademark Office and with other applicable governmental entity or registrar in other jurisdictions outside the United States. From time to time hereafter, and without further consideration, each of the Assignors, the Assignee, and their respective successors and permitted

assigns, covenant and agree that each of the Assignors, the Assignee, and their respective successors and permitted assigns shall execute and deliver, or shall cause to be executed and delivered, such further instruments of conveyance and transfer and take such additional action as the other Party may reasonably request to effect, consummate, confirm, or evidence the transfer to the Assignee, its successors, and permitted assigns of the Acquired Patents in accordance with the foregoing. Assignor shall provide Assignee and its successors and assigns reasonable cooperation and assistance at Assignee's request and expense (including the execution and delivery of any and all country specific forms of assignment, affidavits, declarations, oaths, exhibits, powers of attorney or other documentation) as are reasonably requested by Assignee to effect, record, register or maintain this Assignment and/or the rights assigned herein. The Parties hereby authorize the relevant authority at the United States Patent and Trademark Office and respective foreign patent and trademark offices to record this Agreement and record Assignee as the owner of the Acquired Patents and to issue any and all Acquired Patents to Assignee, as assignee of Assignor's entire right, title and interest in, to and under the same.

3. Power of Attorney. The Assignors hereby constitute and appoint the Assignee as the Assignors' true and lawful attorney in fact, with full power of substitution in the Assignors' name and stead, to take any and all steps, including proceedings at law, in equity or otherwise, to execute, acknowledge and deliver any and all instruments and assurances necessary or expedient in order to vest or perfect the aforesaid rights more effectively in the Assignee or to protect the same or to enforce any claim or right of any kind with respect thereto. The Assignors hereby declare that the foregoing power is coupled with an interest and as such is irrevocable.

4. Notices. All notices, requests, claims, demands or other communications hereunder to any Party shall be given in the manner set forth in the Asset Purchase Agreement. Any Party may change its address for receiving notices, requests, and other documents by giving written notice of such change to the other Parties in accordance with the Asset Purchase Agreement.

5. Severability. If any provision of this Agreement or the application thereof to any Person or circumstance is held invalid or unenforceable, the remainder of this Agreement, and the application of such provision to other Persons or circumstances, shall not be affected thereby, and to such end, the provisions of this Agreement are agreed to be severable.

6. Effectiveness. This Agreement shall be effective as of the Closing Date pursuant to the terms of the Asset Purchase Agreement.

7. Amendments; Waivers. This Agreement may not be waived, altered, amended or modified except by an instrument in writing signed by, or on behalf of each of the Parties hereto.

8. Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed to be an original but all of which shall constitute one and the same agreement.

9. Governing Law; Submission of Jurisdiction; Waiver of Jury Trial. With regard to patent, trademark and copyright issues, this Agreement shall be governed by and construed in accordance with the federal Laws of the United States. For all other matters, this Agreement shall be governed by and construed in accordance with the Laws of the State of Delaware

without regard to the rules of conflict of Laws of the State of Delaware or any other jurisdiction. Each of the Parties irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the Bankruptcy Court for any litigation arising out of or relating to this Agreement and the transactions contemplated thereby (and agrees not to commence any litigation relating thereto except in the Bankruptcy Court), provided, however, that if the Chapter 11 Case has been closed and/or the Bankruptcy Court declines jurisdiction, each of the Parties agree to and hereby irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the United States District Court sitting in Wilmington, Delaware. Each of the Parties irrevocably and unconditionally waives any objection to the laying of venue of any such litigation in any such court. Each Party hereby consents to service of process in the manner set forth in Section 4. EACH PARTY HERETO IRREVOCABLY AND UNCONDITIONALLY WAIVES ANY RIGHT IT MAY HAVE TO A TRIAL BY JURY IN RESPECT OF ANY LITIGATION ARISING OUT OF OR RELATING TO THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREBY.

10. Third Parties. This Agreement will be binding upon, inure to the benefit of and be enforceable by the Parties hereto and their respective successors and permitted assigns and shall not be binding upon, inure to the benefit of, or be enforceable by any other party.

[*Signature Pages Follow*]

IN WITNESS WHEREOF, the Parties have caused this Assignment to be executed by their respective officers thereunto duly authorized as of the date first above written.

ASSIGNORS:

SYNERGY PHARMACEUTICALS INC.

By: _____
Name: Gary G. Gemignani
Title: EVP and Chief Financial Officer

SYNERGY ADVANCED PHARMACEUTICALS, INC.

By: _____
Name: Gary G. Gemignani
Title: EVP and Chief Financial Officer

STATE OF Connecticut)
: ss.: Darien
COUNTY OF Fairfield)

On this 4th day of March 2019, before me personally appeared Gary G Gemignani, in his/her capacity as EVP and CFO of Synergy Pharmaceuticals Inc., and Gary G Gemignani, in his/her capacity as EVP and CFO of Synergy Advanced Pharmaceuticals, Inc.., who each proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is subscribed to or who executed the foregoing instrument in his authorized capacity, and who duly acknowledged to me that execution of the same is his/her own free act and deed and made with appropriate authority.

_____
Notary Public

MICHAEL HENRY BERGMANN
Notary Public
Connecticut
My Commission Expires Mar 31, 2019

My Commission Expires: 03/31/2019

[Notary Seal]

[Signature Page to Patent Assignment – United States]

IN WITNESS WHEREOF, the Parties have caused this Assigment to be executed by their respective officers thereunto duly authorized as of the date first above written.

ASSIGNEE:

BAUSCH HEALTH IRELAND LIMITED

By: _____
Name: Graham Jackson
Title: Director

[Signature Page to Patent Assignment – United States]

Schedule I

Acquired Patents

Title/Mark	Application No.	Application Date	Registration No.	Registration Date	Case Status	Country
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	10/107,814	3/28/2002	7,041,786	5/9/2006	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	11/347,115	2/2/2006	7,799,897	9/21/2010	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	12/763,707	4/20/2010	8,114,831	2/14/2012	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	13/339,785	12/29/2011	8,637,451	1/28/2014	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	14/137,256	12/20/2013			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/133,344	6/4/2008	7,879,802	2/1/2011	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA, ATHEROSCLEROSIS, CORONARY HEART DISEASE, GALLSTONE, OBESITY AND OTHER CARDIOVASCULAR DISEASES	12/630,654	12/3/2009	8,969,514	3/3/2015	Granted	United States of America

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/010,267	1/20/2011	8,716,224	5/6/2014	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/857,283	4/5/2013	8,901,075	12/2/2014	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/528,257	10/30/2014	9,266,926	2/23/2016	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA, ATHEROSCLEROSIS, CORONARY HEART DISEASE, GALLSTONE, OBESITY AND OTHER CARDIOVASCULAR DISEASES	14/742,456	6/17/2015	9,814,752	11/14/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/049,740	2/22/2016	9,914,752	3/13/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/471,462	3/28/2017			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/918,047	3/12/2018			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/228,843	3/28/2014	9,238,677	1/19/2016	Granted	United States of America

METHOD OF INHIBITING BILE ACID ABSORPTION BY ADMINISTERING AN AGONIST OF A GUANYLATE CYCLASE RECEPTOR	13/513,224	12/3/2010	9,089,612	7/28/2015	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/478,505	6/4/2009	8,207,295	6/26/2012	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/467,703	5/9/2012	8,357,775	1/22/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/716,874	12/17/2012	8,497,348	7/30/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/831,293	8/20/2015	9,920,095	3/20/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/504,288	7/16/2009	8,034,782	10/11/2011	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/632,314	2/26/2015	9,505,805	11/29/2016	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/226,300	9/6/2011	8,367,800	2/5/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/731,483	12/31/2012	8,569,246	10/29/2013	Granted	United States of America

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/955,710	7/31/2013	8,664,354	3/4/2014	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	14/301,812	6/11/2014	10,034,836	7/31/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	16/018,278	6/26/2018			Pending	United States of America
PROCESS OF PREPARING GUANYLATE CYCLASE C AGONIST	15/405,787	1/13/2017			Pending	United States of America
PROCESS OF PREPARING GUANYLATE CYCLASE C AGONIST	14/001,638	3/1/2012	9,580,471	2/28/2017	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	14/845,644	9/4/2015	9,610,321	4/4/2017	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/467,631	3/23/2017	9,925,231	3/27/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/467,648	3/23/2017	9,919,024	3/20/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/924,940	3/19/2018			Pending	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	13/421,769	3/15/2012	9,616,097	4/11/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR DOWNREGULATION OF PRO-INFLAMMATORY CYTOKINES	15/026,560	10/9/2014			Pending	United States of America
COMPOSITIONS USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS	14/207,749	3/13/2014	9,486,494	11/6/2016	Granted	United States of America

COMPOSITIONS USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS	15/272,873	9/22/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	14/189,645	2/25/2014	9,545,446	1/17/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	15/381,680	12/16/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	14/207,753	3/13/2014	9,708,367	7/18/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	15/622,526	6/14/2017	10,118,946	11/6/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	16/150,703	10/3/2018			Pending	United States of America
FORMULATIONS AND METHODS FOR TREATING ULCERATIVE COLITIS	16/069,313	1/11/2017			Pending	United States of America
COMPOSITIONS AND METHOD FOR THE TREATMENT AND DETECTION OF COLON CANCER	15/777,273	11/18/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF OPIOID INDUCED DYSFUNCTIONS	15/026,563	10/10/2014			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF OPIOID INDUCED DYSFUNCTIONS	14/944,499	11/18/2015			Pending	United States of America
ULTRA-PURE AGONISTS OF GUANYLATE CYCLASE C, METHOD OF MAKING AND USING SAME	16/000,251	6/5/2018			Pending	United States of America
ULTRA-PURE AGONISTS OF GUANYLATE CYCLASE C, METHOD OF MAKING AND USING SAME	14/896,019	6/5/2014	10,011,637	7/3/2018	Granted	United States of America

INTER PARTES REVIEW OF USP 8,101,579 ENTITLED METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS (IPR 2018-01363)			8,101,579		Pending	United States of America

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	376464-2000US1(00008)

CONFIRMATION NO. 9117

POA ACCEPTANCE LETTER

162421
SAUL EWING ARNSTEIN & LEHR LLP (Bausch Health)
Attn: Patent Docket Clerk, Centre Square West,
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186

OC000000116154033

Date Mailed: 04/13/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/09/2020.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/nrhayden/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/107,814	03/28/2002	Kunwar Shailubhai	SYPA-001/01US 321994-2051

CONFIRMATION NO. 9117

POWER OF ATTORNEY NOTICE

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Date Mailed: 04/13/2020

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/09/2020.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/nrhayden/

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Saul Ewing Arnstein & Lehr LLP (Bausch Health)
Attn: Patent Docket Clerk
Centre Square West
1500 Market Street
38th Floor
Philadelphia, PA 19102-2186

In Re: Patent Term Extension
Application for
U.S. Patent No. 7,041,786

April 13, 2020

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 7,041,786, which claims the human drug product known by the tradename TRULANCE® (plecanatide), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 1,772 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of a request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 1,772 days.

The period of extension set forth in 35 U.S.C. § 156(c) has been calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of December 4, 2018 (83 FR 62590). Under 35 U.S.C. § 156(c):

Period of Extension	=	RRP - PGRRP - DD - ½(TP - PGTP)[1]
	=	3,186 days - 0- 0 - ½(2,829 days - 0)
	=	1,772 days (4.9 years)

Since the regulatory review period began May 2, 2008, after the date that the patent issued (May 9, 2006), the entire regulatory review period has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

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[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

Neither the limitations of 35 U.S.C. § 156(g)(6) nor 35 U.S.C. § 156(c)(3) operate to reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	7,041,786
Granted:	May 9, 2006
Original Expiration Date[2]:	March 25, 2023
Applicant:	Kunwar Shailubhai et al.
Owner of Record:	Synergy Pharmaceuticals, Inc.
Title:	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis
Product Trade Name:	TRULANCE® (plecanatide)
Term Extended:	1,772 days
Expiration Date of Extension:	January 30, 2028

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-7728.

/Raul Tamayo/
Raul Tamayo
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51, Room 6250
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: TRULANCE® (plecanatide)
Docket No.: FDA-2017-E-4282

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Saul Ewing Arnstein & Lehr LLP (Bausch Health)
Attn: Patent Docket Clerk
Centre Square West
1500 Market Street
38th Floor
Philadelphia, PA 19102-2186

In Re: Patent Term Extension
Application for
U.S. Patent No. 7,041,786

October 23, 2020

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 7,041,786 for a period of 1,772 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542, which may be downloaded from the FDA Forms webpage at https://www.fda.gov/about-fda/reports-manuals-forms/forms (https://www.fda.gov/media/69889/download).

Inquiries regarding this communication should be directed to the undersigned by telephone at 571-272-7728, or by email at raul.tamayo@uspto.gov.

/Raul Tamayo/
Raul Tamayo
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue
Bldg. 51, Room 6250
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: TRULANCE® (plecanatide)
Docket No.: FDA-2017-E-4282

UNITED STATES PATENT AND TRADEMARK OFFICE

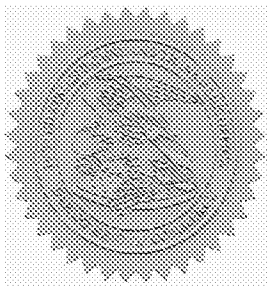
(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	7,041,786
(45)	ISSUED	:	May 9, 2006
(75)	INVENTOR	:	Kunwar Shailubhai et al.
(73)	PATENT OWNER	:	Synergy Pharmaceuticals, Inc.
(95)	PRODUCT	:	TRULANCE® (plecanatide)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 7,041,786 based upon the regulatory review of the product TRULANCE® (plecanatide) by the Food and Drug Administration. According to United States Patent and Trademark Office records, the original expiration date of the patent as of the date of issuance of this certificate is March 25, 2023. Because it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,772 days

subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.



I have caused the seal of the United States Patent and Trademark Office to be affixed this 23rd day of October 2020.

Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,041,786	5/9/2006	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	7,799,897	9/21/2010	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	8,637,451	1/28/2014	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4	9,610,321	4/4/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
5	9,616,097	4/11/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,919,024	3/20/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	9,925,231	3/27/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	10,011,637	7/3/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,041,786	5/9/2006	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	7,799,897	9/21/2010	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	8,637,451	1/28/2014	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4	9,610,321	4/4/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
5	9,616,097	4/11/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Notice of Voluntary Dismissal

CLERK	(BY) DEPUTY CLERK	DATE
John A Cerino		5-6-2021

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
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Page 2 of 2

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,919,024	3/20/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	9,925,231	3/27/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	10,011,637	7/3/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAUSCH HEALTH IRELAND LIMITED, and SALIX PHARMACEUTICALS, INC. Plaintiffs, v. MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. — a VIATRIS COMPANY, Defendants.	C.A. No. 1:21-cv-00611-LPS

NOTICE OF VOLUNTARY DISMISSAL WITHOUT PREJUDICE

Plaintiffs Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc., pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i), hereby voluntarily dismiss this action, without prejudice.

GIBBONS P.C.

By: */s/ Christopher Viceconte*
Christopher Viceconte (No. 5568)
Jennifer M. Rutter (No. 6200)
300 Delaware Avenue, Suite 1015
Wilmington, Delaware 19801
Tel: (302) 518-6322
Fax: (302) 397-2050
cviceconte@gibbonslaw.com
jrutter@gibbonslaw.com

Attorneys for Plaintiffs Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

OF COUNSEL:

Bryan C. Diner
Justin J. Hasford
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Avenue, NW
Washington, DC 20001-4413
Tel: (202) 408-4000

Dated: May 5, 2021