



(51) International Patent Classification:

A61K 39/395 (2006.01) *A61P 1/04* (2006.01)
C12Q 1/68 (2006.01) *G06F 19/20* (2011.01)

(21) International Application Number:

PCT/US2016/062651

(22) International Filing Date:

18 November 2016 (18.11.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/257,173 18 November 2015 (18.11.2015) US

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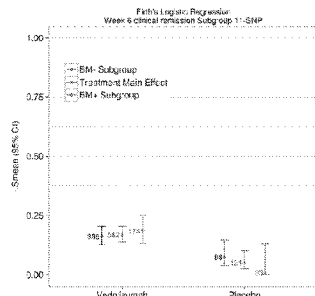
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: METHOD FOR TREATING CROHN'S DISEASE

LS Means Plot for 11-SNP Model on Clinical Remission at Week 6



BM+ subgroup size in Tx arm: 30.96%
BM+ subgroup size overall: 30.31%

Tx OR in BM+ subgroup: 24.98 (1.47, 423.89)
Tx OR in BM- subgroup: 2.37 (1.08, 5.21)
Subgroup interaction p-value: 0.0357
Pseudo R²: 0.106

Subgroup OR comparing BM+ and BM- in Tx arm: 1.17 (0.72, 1.88)

Mean response rate in Tx arm in BM+ subgroup: 0.185 (0.132, 0.252)
Mean response rate in Tx arm in BM- subgroup: 0.161 (0.126, 0.204)
Mean response rate in Tx arm overall: 0.169 (0.138, 0.204)

Within Tx arm:
1.146 times more likely to respond comparing BM+ and BM- subgroup
1.096 times more likely to respond comparing BM+ to overall

*All results based on logistic regression with Firth correction

(57) Abstract: The present invention provides methods for treating Crohn's Disease in an individual. The invention further provides methods for determining if an individual suffering from Crohn's Disease is likely to respond favorably or experience an enhanced treatment effect in response to treatment with vedolizumab. In some embodiments, the methods comprise determining the presence of polymorphisms in the in the TraB Domain Containing 2B (*TRABD2B*) gene and/or the Phosducin (*PDC*) gene and/or the Neuropeptide Y (*NPY*) gene and/or the One Cut Homeobox 1 (*ONECUT1*) gene and/or the Discs, Large Homolog 4 (*DLG4*) gene and/or the Claudin 7 (*CLDN7*) gene and/or the Elongator Acetyltransferase Complex Subunit 5 (*ELP5*) gene.

FIGURE 10



Published:

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

Method for Treating Crohn's Disease

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefits under 35 U.S.C. § 119(e) to U.S. provisional
5 application 62/257,173 filed November 18, 2015, the contents of which are incorporated herein
by reference in their entirety.

BACKGROUND

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the
gastrointestinal tract, and it is characterized by any of the following symptoms: abdominal pain,
10 vomiting, diarrhea, rectal bleeding, severe internal cramps/muscle spasms, tenesmus, fistulae
formation, weight loss, and fever. Crohn's Disease is classified as one of the two main IBDs.

Crohn's Disease is an IBD in which inflammation extends beyond the inner gut lining
and penetrates deeper layers of the intestinal wall of any part of the digestive system. Symptoms
of Crohn's Disease can include any of persistent diarrhea, rectal bleeding, urgent need to move
15 bowels, abdominal cramps and pain, sensation of incomplete evacuation, constipation, fever, loss
of appetite, weight loss, fatigue, night sweats, and loss of menstrual cycle.

Treatment Crohn's Disease typically includes the use of medication such as
aminosalicylates, corticosteroids, immunomodulators, anti-TNF α , or antibiotics; alterations in
diet and nutrition; and, sometimes, surgical procedures. However, it is believed that genetics
20 may play a role in how a treatment regimen affects an individual, although non-genetic variables
may also play a role. As a result, it is difficult to predict the best treatment option for a given
patient with Crohn's Disease. Accordingly, it would be beneficial to devise a method for
identifying subpopulations of patients suffering from Crohn's Disease that are likely to respond
most favorably to a treatment comprising an antagonist of the $\alpha 4\beta 7$ integrin, such as
25 vedolizumab.

SUMMARY

The present invention relates to methods and kits for treating Crohn's Disease in an individual, and for identifying the likelihood that an individual suffering from Crohn's Disease will experience an enhanced treatment effect (e.g., experience an enhanced clinical response or clinical remission) to treatment with an antagonist of the $\alpha 4\beta 7$ integrin, such as an anti- $\alpha 4\beta 7$ antibody (e.g., vedolizumab) and/or experience an enhanced treatment effect when treated with the antagonist. These methods and kits are based on detecting the presence of polymorphisms in, for example, *TRABD2B*, *PDC*, *NPY*, *ONECUT1*, *DLG4*, *CLDN7*, and/or *ELP5* genes.

One aspect of the present invention provides methods for treating Crohn's Disease in an individual, comprising administering an antagonist of the $\alpha 4\beta 7$ integrin, such as an anti- $\alpha 4\beta 7$ antibody (e.g., vedolizumab) to an individual identified as (i) *TRABD2B* variant positive, (ii) *PDC* variant positive, (iii) *NPY* variant positive, (iv) *ONECUT1* variant positive, (v) *DLG4* variant positive, (vi) *CLDN7* variant positive, (vii) *ELP5* variant positive, or (viii) any combination of these.

In some embodiments, the treating comprises remission of Crohn's Disease.

In some embodiments, the individual is heterozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant. In some embodiments, the individual is homozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.

One aspect of the invention comprises methods for determining the likelihood that an individual suffering from Crohn's Disease will experience an enhanced treatment effect when treated with an anti- $\alpha 4\beta 7$ antibody, e.g., vedolizumab, comprising: (i) assaying a biological sample obtained from an individual for the presence or absence of a *TRABD2B* variant and/or a *PDC* variant and/or a *NPY* variant and/or a *ONECUT1* variant and/or a *DLG4* variant and/or a *CLDN7* variant and/or a *ELP5* variant and (ii) detecting the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant, wherein the presence of the

TRABD2B variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant indicates an increased likelihood that the individual will experience an enhanced treatment effect.

Some embodiments comprise methods for determining the likelihood that an individual suffering from Crohn's Disease will respond favorably to treatment with vedolizumab comprising: (i) assaying a biological sample obtained from an individual for the presence or absence of a *TRABD2B* variant and/or a *PDC* variant and/or a *NPY* variant and/or a *ONECUT1* variant and/or a *DLG4* variant and/or a *CLDN7* variant and/or a *ELP5* variant and (ii) detecting the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant, wherein the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant indicates an increased likelihood that the individual will respond favorably to vedolizumab.

In some embodiments, the *TRABD2B* variant is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs6684538, rs17103939, and combinations thereof.

In some embodiments a variant is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs6684538, rs17103939, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the *PDC* variant is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, and combinations thereof.

In some embodiments a variant is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the *NPY* variant is selected from the group consisting of rs16141, rs3779477, rs16129, and combinations thereof.

In some embodiments a variant is selected from the group consisting of rs16141, rs3779477, rs16129, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof

In some embodiments, the *ONECUT1* variant is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, and combinations thereof.

In some embodiments a variant is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the *DLG4* variant is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, and combinations thereof.

In some embodiments a variant is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the *CLDN7* variant or *ELP5* variant is rs2106842, exm1286317, rs2074217, rs222843, and combinations thereof.

In some embodiments a variant is selected from the group consisting of rs2106842, exm1286317, rs2074217, rs222843, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

One aspect of the invention comprises an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been selected for treatment with said antagonist by having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample having been obtained from said subject, wherein said determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist. In some embodiments, the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject is selected for treatment with said $\alpha 4\beta 7$ integrin antagonist by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample having been
5 obtained from said subject, wherein the hereby determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been selected for treatment with said $\alpha 4\beta 7$
10 integrin antagonist by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample having been obtained from said subject, wherein the hereby determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been identified as being eligible for treatment with said $\alpha 4\beta 7$ integrin antagonist by determining the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus, wherein the hereby
15 determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.
20

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject is selected for said treatment by determining or having determined the presence or absence of at least one single nucleotide polymorphism in
25 the *TRABD2B* genomic locus, wherein the hereby determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with inflammatory bowel disease, wherein the subject has been selected by determining the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus, wherein the hereby determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with inflammatory bowel disease, wherein the subject is characterized by the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus and the treatment comprises a step of determining whether the single nucleotide polymorphism in the *TRABD2B* genomic locus is present or absent, wherein the hereby determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

The following aspects of the invention apply to all embodiments of the medical use of the $\alpha 4\beta 7$ integrin antagonist displayed above.

One aspect of the invention comprises a method for predicting a treatment response to an $\alpha 4\beta 7$ integrin antagonist in a subject with Crohn's Disease, said method comprising the step of determining the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a nucleic acid sample obtained from said subject, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

In some embodiments, the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

In some embodiments, at least one single nucleotide polymorphism is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981,

rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939, rs6684538, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the presence or absence of the single nucleotide polymorphisms rs2088361 and rs1556981 has been determined.

5 In some embodiments, the absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

In some embodiments, the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573 has been determined.

10 In some embodiments, the absence of the single nucleotide polymorphisms rs6671927, rs2088361 and rs1556981 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

In some embodiments, the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist, or has been identified as likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy, with the following formula: $Score_i = (0.32 * rs1561573) - (0.4502 * rs6671927) - (0.6524 * rs2088361) - (0.8948 * rs1556981)$, wherein the value for rs1561573, rs6671927, rs2088361 and rs1556981, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.4350 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

20 In some embodiments, the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573 has been determined.

In some embodiments, the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

25 In some embodiments, the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist, or has been identified as likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy, with the following formula: $Score_i = (0.2738 * rs1561573) - (0.3913 * rs6671927) - (0.5404 * rs2088361) - (0.7396 * rs1556981) - (0.1912 * rs11205430)$, wherein the value for rs1561573,

rs6671927, rs2088361, rs1556981 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.3896 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

5 In some embodiments, the presence or absence of the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, and rs11211632 has been determined.

In some embodiments, the absence of the single nucleotide polymorphisms rs11211613, rs12061891, rs11211632 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

10 In some embodiments, the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist, or has been identified as likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy, with the following formula: $Score_i = (0.2865 * rs1561573) - (0.3678 * rs11211613) - (1.0079 * rs12061891) - (0.5831 * rs11211632) - (0.2351 * rs11205430)$, wherein the value for rs1561573, rs11211613, rs12061891, rs11211632 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.5910 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

20 In some embodiments, the presence or absence of at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* has additionally been determined.

In some embodiments, the presence or absence of at least one single nucleotide polymorphism in each of the genomic loci of *TRABD2B*, *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* has been determined.

25 In some embodiments, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926, rs11801527, rs12407957, and rs10798041.

In some embodiments, the single nucleotide polymorphism is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

5 In some embodiments, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129.

In some embodiments, the single nucleotide polymorphism is selected from the group consisting of rs16141, rs3779477, rs16129, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

10 In some embodiments, the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, and rs2456525.

In some embodiments, the single nucleotide polymorphism is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

15 In some embodiments, the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229.

20 In some embodiments, the single nucleotide polymorphism is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the single nucleotide polymorphism in the *ELP5* genomic locus is rs2106842, exm1286317, rs2074217, and rs222843.

25 In some embodiments, the single nucleotide polymorphism is rs2106842, exm1286317, rs2074217, rs222843, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the presence or absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842 has been determined.

In some embodiments, the absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

In some embodiments, the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist, or has been identified as likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy, with the following formula: $Score_i = (-0.1797 * rs7543124) - (0.3707 * rs6671927) - (0.5741 * rs2088361) - (0.5848 * rs1556981) + (0.7127 * rs1882926) - (0.7024 * rs11801527) - (0.6841 * rs3779477) + (0.2158 * rs2440335) + (0.6147 * rs1899750) + (0.3475 * rs1875673) + (0.397 * rs2106842)$, wherein the value for rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.2123 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

In some embodiments, the presence or absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 has been determined.

In some embodiments, the absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs1899750 and rs2106842 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

In some embodiments, the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist, or has been identified as likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy, with the following formula: $Score_i = (-0.2213 * rs7543124) - (0.8735 * rs2088361) - (0.659 * rs1556981) + (0.8567 * rs1882926) - (0.858 * rs11801527) - (0.6935 * rs3779477) + (0.9288 * rs1899750) + (0.7159 * rs2106842)$, wherein the value for rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842, respectively, is 2 if the single

nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.6803 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

5 Some embodiments comprise detecting the presence of the *TRABD2B* variant. Some embodiments comprise detecting the presence of rs1556981, rs2088361, rs1561573, and rs6671927 variants. Some embodiments comprise detecting the presence of rs1556981, rs2088361, rs1561573, rs6671927, and rs11205430 variants. Some embodiments comprise detecting the presence of rs1561573, rs11211613, rs12061891, rs11211632, and rs11205430.

10 Some embodiments comprise detecting the presence of the *TRABD2B* variant, the *PDC* variant, the *NPY* variant, the *ONECUTI* variant, *CLDN7* variant, and the *ELP5* variant. Some embodiments comprise detecting the presence of rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842 variants.

15 Some embodiments comprise detecting the presence of the *TRABD2B* variant, the *PDC* variant, the *NPY* variant the *ONECUTI* variant, the *DLG4* variant, the *CLDN7* variant, and the *ELP5* variant. Some embodiments comprise detecting the presence of rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842 variants.

20 One aspect of the invention comprises a group of biomarkers comprising SNP rs2088361 and SNP rs1556981.

 In some embodiments, a group of biomarkers comprises SNP rs2088361, SNP rs1556981, and at least two SNPs selected from the group consisting of rs7543124, rs6671927, rs1561573 and rs11205430.

25 In some embodiments, a group of biomarkers consists of SNPs rs6671927, rs2088361, rs1556981 and rs1561573.

 In some embodiments, a group of biomarkers consists of SNPs rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573.

In some embodiments, a group of biomarkers comprises SNP rs2088361, SNP rs1556981, and SNPs rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842.

5 In some embodiments, a group of biomarkers consists of SNPs rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842.

In some embodiments, a group of biomarkers comprises SNP rs2088361, SNP rs1556981, and SNPs rs7543124, rs11801527, rs3779477, rs1882926, rs1899750, and rs2106842.

10 In some embodiments, the group of biomarkers consists of SNPs rs2088361, rs1556981, rs7543124, rs11801527, rs3779477, rs1882926, rs1899750, and rs2106842.

In some embodiments, a group of biomarkers comprises SNPs rs11205430, rs1561573, rs11211613, rs12061891 and rs11211632.

15 One aspect of the invention comprises kits, such as kits comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs1556981, rs2088361, rs1561573, and rs6671927, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

20 In some embodiments, the kits comprise: a pair of primers that specifically hybridizes to rs1556981; a pair of primers that specifically hybridizes to rs2088361; a pair of primers that specifically hybridizes to rs1561573; and a pair of primers that specifically hybridizes to rs6671927.

25 In some embodiments, the kits comprise: a pair of primers that specifically hybridizes to rs1556981; a pair of primers that specifically hybridizes to rs2088361; a pair of primers that specifically hybridizes to rs1561573; a pair of primers that specifically hybridizes to rs6671927; and a pair of primers that specifically hybridizes to rs11205430.

In some embodiments, the kits comprise: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs1561573,

rs11211613, rs12061891, rs11211632, and rs11205430, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

In some embodiments, the kits comprise: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842, and (ii) a
5 detectably labeled probe that hybridizes to the genetic variant.

In some embodiments, the kits comprise: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842, and (ii) a detectably labeled probe that hybridizes to the genetic
10 variant.

One aspect of the invention comprises a kit, diagnostic composition or device comprising a probe selective for at least one single nucleotide polymorphism in the *TRABD2B* genomic locus. In some embodiments, the at least one single nucleotide polymorphism in the *TRABD2B*
15 genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

Some embodiments of the kit, diagnostic composition or device comprise a probe selected for at least one single nucleotide polymorphism selected from the group consisting of
20 rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939, rs6684538, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the kit, diagnostic composition or device comprises probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and
25 rs1561573.

In some embodiments, the kit, diagnostic composition or device comprises probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573.

In some embodiments, the kit, diagnostic composition or device comprises probes selective for the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632.

5 In some embodiments, the kit, diagnostic composition or device further comprises a probe selective for at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

In some embodiments, the kit, diagnostic composition or device further comprises probes selective for at least one single nucleotide polymorphism in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

10 In some embodiments of the kit, diagnostic composition, or device, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926, rs11801527, rs12407957, and rs10798041. For example, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926 and rs11801527.

15 Some embodiments of the kit, diagnostic composition, or device comprise probes selected for at least one single nucleotide polymorphism selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

20 In some embodiments of the kit, diagnostic composition, or device, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129. For example, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141 and rs3779477.

25 Some embodiments of the kit, diagnostic composition, or device comprise probes selected for at least one single nucleotide polymorphism selected from the group consisting of rs16141, rs3779477, rs16129, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the kit, diagnostic composition, or device, the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, and rs2456525. For example, the

single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750 and rs7180600.

Some embodiments of the kit, diagnostic composition, or device comprise probes selected for at least one single nucleotide polymorphism selected from the group consisting of
5 rs16141, rs3779477, rs16129, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the kit, diagnostic composition, or device, the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229. For example, the single nucleotide
10 polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408 and rs1875673.

Some embodiments of the kit, diagnostic composition, or device comprise probes selected for at least one single nucleotide polymorphism selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, SNPs in linkage
15 disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the kit, diagnostic composition, or device, the single nucleotide polymorphism in the *ELP5* genomic locus is rs2106842, exm1286317, rs2074217, and rs222843. For example, the single nucleotide polymorphism in the *ELP5* genomic locus is rs2106842.

Some embodiments of the kit, diagnostic composition, or device comprise probes
20 selected for at least one single nucleotide polymorphism selected from the group consisting of rs2106842, exm1286317, rs2074217, rs222843, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the kit, diagnostic composition comprises probes selective for the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926,
25 rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842.

In some embodiments, the kit, diagnostic composition or device comprises probes selective for the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842.

In some embodiments, the kit, diagnostic composition or device further comprises an enzyme for primer elongation, nucleotides and/or labeling agents.

On aspect of the invention comprises a microarray comprising a probe selective for at least one single nucleotide polymorphism in the *TRABD2B* genomic locus. In some
5 embodiments, the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

In some embodiments, the microarray comprises probes selective for the single
10 nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573.

In some embodiments, the microarray comprises probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573.

In some embodiments, the microarray comprises probes selective for the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632.

15 In some embodiments, the microarray further comprises a probe selective for at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

In some embodiments, the microarray further comprises probes selective for the single nucleotide polymorphisms in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and
20 *ELP5*.

In some embodiments of the microarray, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926, rs11801527, rs12407957, and rs10798041. For example, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926 and rs11801527.

25 In some embodiments of the microarray, the single nucleotide polymorphism is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the microarray, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129. For example, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141 and rs3779477.

5 In some embodiments of the microarray, the single nucleotide polymorphism is selected from the group consisting of rs16141, rs3779477, rs16129, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the microarray, the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, 10 rs1899750, rs7180600, rs2456507, and rs2456525. For example, the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750 and rs7180600.

In some embodiments of the microarray, the single nucleotide polymorphism is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, 15 rs2456525, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the microarray, the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229. For example, the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, 20 rs3826408 and rs1875673.

In some embodiments of the microarray, the single nucleotide polymorphism is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments of the microarray, the single nucleotide polymorphism in the *ELP5* 25 genomic locus is selected from the group consisting of rs2106842, exm1286317, rs2074217, and rs222843. For example, the single nucleotide polymorphism in the *ELP5* genomic locus is rs2106842.

In some embodiments of the microarray, the single nucleotide polymorphism is selected from the group consisting of rs2106842, exm1286317, rs2074217, rs222843, SNPs in linkage disequilibrium with any of the foregoing, and combinations thereof.

In some embodiments, the microarray comprises probes selective for the single
5 nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842.

In some embodiments, the microarray comprises probes selective for the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 is determined.

10 One aspect of the invention comprises the use of the group of biomarkers, the kit, diagnostic composition or device, or the microarray as described herein for predicting a patient's response to treatment with a $\alpha 4\beta 7$ integrin antagonist. In some embodiments, the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

In some embodiments, the use of the group of biomarkers, the kit, diagnostic composition
15 or device, or the microarray as described herein for identifying a patient with Crohn's Disease as being eligible for treatment with a $\alpha 4\beta 7$ integrin antagonist. In some embodiments, the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a summary of the genotype of individuals in clinical trials discussed in
20 the Examples, after applying Quality Control (QC) procedures (1A), and baseline characteristics of individuals in the clinical trials discussed in the Examples (1B).

Figure 2 shows the top 10 genes whose SNPs are associated with clinical remission of Crohn's Disease, as determined via a gene-level scan, in all individuals across multiple clinical trials (2A), in clinical trial C13007 (2B), and in clinical trial C13011 (2C); and in Caucasians
25 across multiple clinical trials (2D).

Figure 3 shows the top 10 genes whose SNPs are associated with enhanced clinical response of vedolizumab in Crohn's Disease patients, as determined via a gene-level scan, in all

individuals across multiple clinical trials (3A), in clinical trial C13007 (3B), and in clinical trial C13011 (3C); and in Caucasians across multiple clinical trials (3D).

Figure 4 depicts a least square (LS) means plot for predicted clinical remission of Crohn's disease using a 19-SNP model.

Figure 5 provides graphic data showing clinical remission or enhanced clinical response in individuals with Crohn's Disease following administration of vedolizumab using an 11-SNP model. Figure 5A depicts a LS means plot showing clinical remission of Crohn's Disease in individuals treated with vedolizumab vs. placebo; Figure 5B shows clinical remission over time in clinical trial C13007; Figure 5C shows clinical remission over time in clinical trial C13011; Figure 5D depicts a LS means plot showing enhanced clinical response to vedolizumab vs. placebo in individuals with Crohn's Disease; Figure 5E shows enhanced clinical response over time in clinical trial C13007; Figure 5F shows enhanced clinical response over time in clinical trial C13011; Figure 5G depicts plots of Crohn's Disease Activity Index (CDAI) score vs. genetic biomarker scores in patients treated with vedolizumab and placebo; and Figure 5H depicts a plot of the observed CDAIs vs. the predicted CDAI based on the 11-SNP genetic score.

Figure 6 depicts a LS means plot for predicted clinical remission of Crohn's disease using an 8-SNP model.

Figure 7 provides graphic data showing clinical remission or enhanced clinical response in individuals with Crohn's Disease following administration of vedolizumab using a 4-SNP model. Figure 7A depicts a LS means plot showing clinical remission of Crohn's Disease in individuals treated with vedolizumab vs. placebo; Figure 7B shows clinical remission over time in clinical trial C13007; Figure 7C shows clinical remission over time in clinical trial C13011; Figure 7D depicts a LS means plot showing enhanced clinical response to vedolizumab vs. placebo in individuals with Crohn's Disease; Figure 7E shows enhanced clinical response over time in clinical trial C13007; Figure 7F shows enhanced clinical response over time in clinical trial C13011; Figure 7G depicts plots of CDAI score vs. genetic biomarker scores in patients treated with vedolizumab and placebo; and Figure 7H depicts a plot of the observed CDAIs vs. the predicted CDAI based on the 4-SNP genetic score.

Figure 8 depicts a LS means plot for predicted clinical remission of Crohn's disease using a first 5-SNP model (8A) and a second 5-SNP model (8B).

Figure 9 shows a summary of demographic differences between cohorts 1 and 2 in the C13007 clinical trial (9A-B) and a summary of clinical characteristics in cohorts 1 and 2 of the C13007 clinical trial (9C).

Figure 10 depicts a LS means plot showing replication data with the 11-SNP model for predicted clinical remission of Crohn's disease.

DETAILED DESCRIPTION

Provided herein are methods for treating Crohn's Disease. In some embodiments, the individual is suffering from or has been diagnosed with Crohn's Disease. Also described herein are methods for identifying an individual suffering from Crohn's Disease that will likely respond favorably to treatment, *e.g.*, by blocking $\alpha 4\beta 7$ integrin signaling with $\alpha 4\beta 7$ integrin direct binding agents. In some embodiments, the methods comprise identifying an individual that will respond favorably to treatment with an anti-integrin antibody, selected from the group consisting of vedolizumab, natalizumab, etrolizumab, and AMG181, or an anti- $\alpha 4\beta 7$ ligand antibody (such as an antibody that binds MAdCAM-1) including binding agents such as PF-547659. Methods for identifying an individual who will likely experience an enhanced treatment response to, *e.g.*, vedolizumab, natalizumab, etrolizumab, AMG181, and/or $\alpha 4\beta 7$ ligand (MAdCAM-1) binding agents such as PF-547659 as compared to another individual are also described herein.

Target Population

The present inventors surprisingly discovered that individuals suffering from Crohn's Disease who possess a *TRABD2B* variant, a *CLDN7* variant, a *GABARAP* variant, an *ELP5* variant, a *CTDNEP1* variant, a *PDC* variant, a *DLG4* variant, a *MIR324* variant, a *ONECUT1* variant, and/or a *NPY* variant are more likely to experience clinical remission and/or an enhanced treatment response, *e.g.*, to vedolizumab, than individuals without the variants. The present inventors also surprisingly discovered that individuals suffering from Crohn's Disease who

possess a *C5orf20* variant, a *CLN5* variant, a *COL24A1* variant, a *TIFAB* variant, a *PLAGL1* variant, a *CEP72* variant, a *FBXL3* variant, a *PAPOLG* variant, a *SLC47A1* variant, and/or a *WRAP53* variant are more likely to experience clinical remission and/or an enhanced treatment response, *e.g.*, to vedolizumab, than individuals without the variants. In some embodiments, the variants described herein are germline mutations and/or mutations in non-translated gene regions. In some embodiments, the mutations are located at the UTR region of a gene.

In some embodiments, an individual suffering from Crohn's Disease who possesses a *TRABD2B* variant, a *PDC* variant, a *NPY* variant, a *ONECUT1* variant, a *DLG4* variant, a *CLDN7* variant, and/or a *ELP5* variant is more likely to experience an enhanced treatment response, *e.g.*, to an anti- $\alpha 4\beta 7$ antibody, *e.g.*, to vedolizumab, than individuals without any of the variants. Individuals with variants as disclosed herein are likely to respond favorably to a treatment regimen administered to mitigate or cause remission of Crohn's Disease. In some embodiments, the treatment comprises administration of vedolizumab. Unless otherwise noted, SNP positions disclosed herein are based on Genome Reference Consortium Human Genome Build GRCh37.

As used herein, "*TRABD2B*" refers to TraB Domain Containing 2B gene, which is located on chromosome 1. The start and end positions are located at 48,221,199 and 48,467,562. Hence, the *TRABD2B* genomic locus extends from position 48,221,199 to position 48,467,562 on chromosome 1. An exemplary gene sequence is Gene ID: 388630.

As used herein, "*TRABD2B* variant" is a *TRABD2B* gene with a sequence identity that is less than 100% identical to that of Gene ID: 388630. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 388630, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 388630. In some embodiments, a *TRABD2B* variant is a *TRABD2B* polynucleotide that exhibits at least one polymorphism in the *TRABD2B* coding region as compared to the coding region of Gene ID: 388630. In some embodiments, a *TRABD2B* variant is associated with a favorable response to $\alpha 4\beta 7$ antagonist treatment, such as an anti- $\alpha 4\beta 7$ antibody, such as vedolizumab. In some embodiments, a *TRABD2B* variant that is associated

with a favorable response to treatment, such as vedolizumab, is selected from the group consisting of rs7543124 (position 48227135, alleles A/G), rs6671927 (position 48285768, alleles C/T), rs12134443 (position 48286563, alleles T/C), rs11211624 (position 48359634, alleles G/T), rs2088361 (position 48362713, alleles G/A), rs1556981 (position 48370525, alleles T/C),
 5 rs11205430 (position 48442182, alleles A/G), rs1561573 (position 48227943, alleles T/C), rs11211613 (position 48290860, alleles A/C), rs12061891 (position 48392033, alleles T/C), rs11211632 (position 48406460, alleles A/G), rs17103939 (position 48409812, alleles T/C), rs6684538 (position 48380390, alleles A/G), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in linkage disequilibrium with one or more *TRABD2B*
 10 variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 .

An individual who is heterozygous or homozygous for a *TRABD2B* variant is “*TRABD2B* variant positive.”

The single nucleotide polymorphism in the *TRABD2B* genomic locus is, for example, selected from the group consisting of:

- 15 • SNP rs7543124 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 1, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs6671927 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 2, wherein in one or two alleles of the wild-type nucleotide C is replaced by
 20 indicator nucleotide T,
- SNP rs12134443 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 3, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs11211624 which is represented by a single polymorphic change at position 26 of
 25 SEQ ID NO: 4, wherein in one or two alleles of the wild-type nucleotide G is replaced by indicator nucleotide T,

- SNP rs2088361 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 5, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G,
- 5 • SNP rs1556981 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 6, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs11205430 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 7, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G,
- 10 • SNP rs1561573 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 8, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs11211613 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 9, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide C,
- 15 • SNP rs12061891 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 10, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs11211632 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 11, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G,
- 20 • SNP rs17103939 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 12, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T, and
- 25 • SNP rs6684538 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 13, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G.

As used herein, “*PDC*” refers to the Phosducin gene, which is located on chromosome 1. The start and end positions are located at 186,407,697 and 186,435,240. Hence, the *PDC* genomic locus extends from position 186,407,697 to position 186,435,240 on chromosome 1. An exemplary gene sequence is Gene ID: 5132.

As used herein, “*PDC* variant” is a *PDC* gene with a sequence identity that is less than 100% identical to that of Gene ID: 5132. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 5132, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 5132. In some embodiments, a *PDC* variant is a *PDC* polynucleotide that exhibits at least one polymorphism in the *PDC* coding region as compared to the coding region of Gene ID: 5132. In some embodiments, a *PDC* variant is associated with a favorable response to treatment, such as vedolizumab. In some embodiments, a *PDC* variant that is associated with a favorable response to treatment, such as vedolizumab, is selected from the group consisting of rs1882926 (position 186411579, alleles A/C), rs11801527 (position 186418798, alleles A/G), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in linkage disequilibrium with one or more *PDC* variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 , such as rs12407957 and rs10798041.

An individual who is heterozygous or homozygous for a *PDC* variant is “*PDC* variant positive.”

The single nucleotide polymorphism in the *PDC* genomic locus is, for example, selected from the group consisting of:

- SNP rs1882926 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 14, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide C, and
- SNP rs11801527 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 15, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G.

As used herein, “*NPY*” refers to the Neuropeptide Y gene, which is located on chromosome 7. The start and end positions are located at 24,318,806 and 24,336,484. Hence, the *NPY* genomic locus extends from position 24,318,806 to position 24,336,484 on chromosome 7. An exemplary gene sequence is Gene ID: 4852.

As used herein, “*NPY* variant” is a *NPY* gene with a sequence identity that is less than 100% identical to that of Gene ID: 4852. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 4852, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 4852. In some embodiments, a *NPY* variant is a *NPY* polynucleotide that exhibits at least one polymorphism in the *NPY* coding region as compared to the coding region of Gene ID: 4852. In some embodiments, a *NPY* variant is associated with a favorable response to treatment, such as vedolizumab. In some embodiments, a *NPY* variant that is associated with a favorable response to treatment, such as vedolizumab, is selected from the group consisting of rs16141 (position 24324759, alleles A/C), rs3779477 (position 24327526, alleles T/C), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in linkage disequilibrium with one or more *NPY* variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 , such as rs16129.

An individual who is heterozygous or homozygous for a *NPY* variant is “*NPY* variant positive.”

The single nucleotide polymorphism in the *NPY* genomic locus is, for example, selected from the group consisting of:

- SNP rs16141 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 16, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide C, and
- SNP rs3779477 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 17, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T.

As used herein, “*ONECUTI*” refers to the One Cut Homeobox 1 gene, which is located on chromosome 15. The start and end positions are located at 53,044,159 and 53,087,209. Hence, the *ONECUTI* genomic locus extends from position 53,044,159 to position 53,087,209 on chromosome 15. An exemplary gene sequence is Gene ID: 3175.

As used herein, “*ONECUTI* variant” is a *ONECUTI* gene with a sequence identity that is less than 100% identical to that of Gene ID: 3175. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 3175, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 3175. In some embodiments, a *ONECUTI* variant is a *ONECUTI* polynucleotide that exhibits at least one polymorphism in the *ONECUTI* coding region as compared to the coding region of Gene ID: 3175. In some embodiments, a *ONECUTI* variant is associated with a favorable response to treatment, such as vedolizumab. In some embodiments, a *ONECUTI* variant that is associated with a favorable response to treatment, such as vedolizumab, is selected from the group consisting of rs2440335 (position 53046210, alleles G/A), rs2440332 (position 53050252, alleles T/C), rs1899750 (position 53068506, alleles C/T), rs7180600 (position 53070141, alleles A/G), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in linkage disequilibrium with one or more *ONECUTI* variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 , such as rs2456507 and rs2456525.

An individual who is heterozygous or homozygous for a *ONECUTI* variant is “*ONECUTI* variant positive.”

The single nucleotide polymorphism in the *ONECUTI* genomic locus is, for example, selected from the group consisting of:

- SNP rs2440335 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 18, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs2440332 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 19, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1899750 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 20, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T, and
- SNP rs7180600 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 21, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G.

As used herein, “*DLG4*” refers to the Discs, Large Homolog 4 gene, which is located on chromosome 15. The start and end positions are located at 7,088,209 and 7,128,369. Hence, the *DLG4* genomic locus extends from position 7,088,209 to position 7,128,369 on chromosome 15. An exemplary gene sequence is Gene ID: 1742.

As used herein, “*DLG4* variant” is a *DLG4* gene with a sequence identity that is less than 100% identical to that of Gene ID: 1742. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 1742, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 1742. In some embodiments, a *DLG4* variant is a *DLG4* polynucleotide that exhibits at least one polymorphism in the *DLG4* coding region as compared to the coding region of Gene ID: 1742. In some embodiments, a *DLG4* variant is associated with a favorable response to treatment, such as vedolizumab. In some embodiments, a *DLG4* variant that is associated with a favorable response to treatment, such as vedolizumab, is selected from the group consisting of rs17203281 (position 7099811, alleles A/G), rs3826408 (position 7101292, alleles T/C), rs1875673 (position 7108506, alleles T/G), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in linkage disequilibrium with one or more *DLG4* variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 , such as rs739669, rs2017365, and rs929229.

An individual who is heterozygous or homozygous for a *DLG4* variant is “*DLG4* variant positive.”

The single nucleotide polymorphism in the *DLG4* genomic locus is, for example, selected from the group consisting of:

- SNP rs17203281 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 22, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3826408 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 23, wherein in one or two alleles of the wild-type nucleotide C is replaced by indicator nucleotide T, and
- SNP rs1875673 which is represented by a single polymorphic change at position 26 of SEQ ID NO: 24, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide T or G.

As used herein, “*CLDN7*” refers to the Claudin 7 gene, which is located on chromosome 17. The start and end positions are located at 7,158,221 and 7,171,512. Hence, the *CLDN7* genomic locus extends from position 7,158,221 to position 7,171,512 on chromosome 17. An exemplary gene sequence is Gene ID: 1366.

As used herein, “*CLDN7* variant” is a *CLDN7* gene with a sequence identity that is less than 100% identical to that of Gene ID: 1366. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 1366, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 1366. In some embodiments, a *CLDN7* variant is a *CLDN7* polynucleotide that exhibits at least one polymorphism in the *CLDN7* coding region as compared to the coding region of Gene ID: 1366. In some embodiments, a *CLDN7* variant is associated with a favorable response to treatment, such as vedolizumab. In some embodiments, a *CLDN7* variant that is associated with a favorable response to treatment, such as vedolizumab, is rs2106842 (position 7162451, alleles G/A), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in

linkage disequilibrium with one or more *CLDN7* variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 , such as exm1286317, rs2074217, and rs222843.

An individual who is heterozygous or homozygous for a *CLDN7* variant is “*CLDN7* variant positive.”

5 As used herein, “*ELP5*” refers to the Elongator Acetyltransferase Complex Subunit 5 gene, which is located on chromosome 17. The start and end positions are located at 7,150,371 and 7,168,259. Hence, the *ELP5* genomic locus extends from position 7,150,371 to position 7,168,259 on chromosome 17. An exemplary gene sequence is Gene ID: 23587.

10 As used herein, “*ELP5* variant” is a *ELP5* gene with a sequence identity that is less than 100% identical to that of Gene ID: 23587. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 23587, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 23587. *ELP5* overlaps with *CLDN7* and, therefore, in some embodiments an *ELP5* variant is also a *CLDN7* variant. Thus, in some embodiments, a single variant can be both an *ELP5* variant and a *CLDN7* variant. In some embodiments, a *ELP5* variant is a *ELP5* polynucleotide that exhibits at least one polymorphism in the *ELP5* coding region as compared to the coding region of Gene ID: 23587. In some embodiments, a *ELP5* variant is associated with a favorable response to treatment, such as vedolizumab. In some embodiments, a *ELP5* variant that is associated with a favorable response to treatment, such as vedolizumab, is rs2106842 (position 15 7162451, alleles G/A), variants in linkage disequilibrium with any of these, and combinations thereof. Variants in linkage disequilibrium with one or more *ELP5* variants disclosed herein include any variant with a r^2 value ≥ 0.8 , ≥ 0.9 , or ≥ 0.95 , such as rs2074217, rs222843, and exm1286317. 20

An individual who is heterozygous or homozygous for a *ELP5* variant is “*ELP5* variant positive.” 25

The single nucleotide polymorphism in the *ELP5* genomic locus is, for example, SNP rs2106842 which is represented by a single polymorphic change at position 26 of SEQ ID NO:

25, wherein in one or two alleles of the wild-type nucleotide A is replaced by indicator nucleotide G.

As used herein, “*GABARAP*” refers to the GABA(A) Receptor-Associated Protein gene, which is located on chromosome 17. The start and end positions are located at 7,138,737 and 7,150,753. An exemplary gene sequence is Gene ID: 11337.

As used herein, “*GABARAP* variant” is a *GABARAP* gene with a sequence identity that is less than 100% identical to that of Gene ID: 11337. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 11337, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 11337. In some embodiments, a *GABARAP* variant is a *GABARAP* polynucleotide that exhibits at least one polymorphism in the *GABARAP* coding region as compared to the coding region of Gene ID: 11337. In some embodiments, a *GABARAP* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *GABARAP* variant is “*GABARAP* variant positive.”

As used herein, “*CTDNEP1*” refers to the CTD Nuclear Envelope Phosphatase 1 gene, which is located on chromosome 17. The start and end positions are located at 7,141,905 and 7,160,259. An exemplary gene sequence is Gene ID: 23399.

As used herein, “*CTDNEP1* variant” is a *CTDNEP1* gene with a sequence identity that is less than 100% identical to that of Gene ID: 23399. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 23399, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 23399. In some embodiments, a *CTDNEP1* variant is a *CTDNEP1* polynucleotide that exhibits at least one polymorphism in the *CTDNEP1* coding region as compared to the coding region of Gene ID: 23399. In some embodiments, a *CTDNEP1* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *CTDNEP1* variant is “*CTDNEP1* variant positive.”

As used herein, “*MIR324*” refers to the MicroRNA 324 gene, which is located on chromosome 17. The start and end positions are located at 7,121,615 and 7,131,698. An exemplary gene sequence is Gene ID: 442898.

As used herein, “*MIR324* variant” is a *MIR324* gene with a sequence identity that is less than 100% identical to that of Gene ID: 442898. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 442898, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 442898. In some embodiments, a *MIR324* variant is a *MIR324* polynucleotide that exhibits at least one polymorphism in the *MIR324* coding region as compared to Gene ID: 442898. In some embodiments, a *MIR324* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *MIR324* variant is “*MIR324* variant positive.”

As used herein, “*C5orf20*” refers to the Chromosome 5 Open Reading Frame 20 gene (dendritic cell-associated nuclear protein, DCANP1), which is located on chromosome 5. The start and end positions are located at 134,774,903 and 134,788,038. An exemplary gene sequence is Gene ID: 140947.

As used herein, “*C5orf20* variant” is a *C5orf20* gene with a sequence identity that is less than 100% identical to that of Gene ID: 140947. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 140947, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 140947. In some embodiments, a *C5orf20* variant is a *C5orf20* polynucleotide that exhibits at least one polymorphism in the *C5orf20* coding region as compared to the coding region of Gene ID: 140947. In some embodiments, a *C5orf20* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *C5orf20* variant is “*C5orf20* variant positive.”

As used herein, “*CLN5*” refers to the Ceroid-Lipofuscinosis, Neuronal 5 gene, which is located on chromosome 13. The start and end positions are located at 77,561,058 and 77,581,652. An exemplary gene sequence is Gene ID: 1203.

As used herein, “*CLN5* variant” is a *CLN5* gene with a sequence identity that is less than 100% identical to that of Gene ID: 1203. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 1203, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 1203. In some embodiments, a *CLN5* variant is a *CLN5* polynucleotide that exhibits at least one polymorphism in the *CLN5* coding region as compared to the coding region of Gene ID: 1203. In some embodiments, a *CLN5* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *CLN5* variant is “*CLN5* variant positive.”

As used herein, “*COL24A1*” refers to the Collagen, Type XXIV, Alpha 1 gene, which is located on chromosome 1. The start and end positions are located at 86,189,915 and 86,627,121. An exemplary gene sequence is Gene ID: 255631.

As used herein, “*COL24A1* variant” is a *COL24A1* gene with a sequence identity that is less than 100% identical to that of Gene ID: 255631. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 255631, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 255631. In some embodiments, a *COL24A1* variant is a *COL24A1* polynucleotide that exhibits at least one polymorphism in the *COL24A1* coding region as compared to the coding region of Gene ID: 255631. In some embodiments, a *COL24A1* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *COL24A1* variant is “*COL24A1* variant positive.”

As used herein, “*TIFAB*” refers to the TRAF-Interacting Protein With Forkhead-Associated Domain, Family Member B gene, which is located on chromosome 5. The start and

end positions are located at 134,779,557 and 134,793,089. An exemplary gene sequence is Gene ID: 497189.

As used herein, “*TIFAB* variant” is a *TIFAB* gene with a sequence identity that is less than 100% identical to that of Gene ID: 497189. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 497189, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 497189. In some embodiments, a *TIFAB* variant is a *TIFAB* polynucleotide that exhibits at least one polymorphism in the *TIFAB* coding region as compared to the coding region of Gene ID: 497189. In some embodiments, a *TIFAB* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *TIFAB* variant is “*TIFAB* variant positive.”

As used herein, “*PLAGL1*” refers to the Pleiomorphic Adenoma Gene-Like 1 gene, which is located on chromosome 6. The start and end positions are located at 144,256,436 and 144,390,735. An exemplary gene sequence is Gene ID: 5325.

As used herein, “*PLAGL1* variant” is a *PLAGL1* gene with a sequence identity that is less than 100% identical to that of Gene ID: 5325. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 5325, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 5325. In some embodiments, a *PLAGL1* variant is a *PLAGL1* polynucleotide that exhibits at least one polymorphism in the *PLAGL1* coding region as compared to the coding region of Gene ID: 5325. In some embodiments, a *PLAGL1* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *PLAGL1* variant is “*PLAGL1* variant positive.”

As used herein, “*CEP72*” refers to the Centrosomal Protein 72kDa gene, which is located on chromosome 5. The start and end positions are located at 607,404 and 658,666. An exemplary gene sequence is Gene ID: 55722.

As used herein, “*CEP72* variant” is a *CEP72* gene with a sequence identity that is less than 100% identical to that of Gene ID: 55722. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 55722, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 55722. In some embodiments, a *CEP72* variant is a *CEP72* polynucleotide that exhibits at least one polymorphism in the *CEP72* coding region as compared to the coding region of Gene ID: 55722. In some embodiments, a *CEP72* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *CEP72* variant is “*CEP72* variant positive.”

As used herein, “*FBXL3*” refers to the F-Box And Leucine-Rich Repeat Protein 3 gene, which is located on chromosome 13. The start and end positions are located at 77,574,388 and 77,606,331. An exemplary gene sequence is Gene ID: 26224.

As used herein, “*FBXL3* variant” is a *FBXL3* gene with a sequence identity that is less than 100% identical to that of Gene ID: 26224. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 26224, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 26224. In some embodiments, a *FBXL3* variant is a *FBXL3* polynucleotide that exhibits at least one polymorphism in the *FBXL3* coding region as compared to the coding region of Gene ID: 26224. In some embodiments, a *FBXL3* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *FBXL3* variant is “*FBXL3* variant positive.”

As used herein, “*PAPOLG*” refers to the Poly(A) Polymerase Gamma gene, which is located on chromosome 2. The start and end positions are located at 60,978,364 and 61,034,221. An exemplary gene sequence is Gene ID: 64895.

As used herein, “*PAPOLG* variant” is a *PAPOLG* gene with a sequence identity that is less than 100% identical to that of Gene ID: 64895. In some embodiments, the variant has a

sequence identity that is from about 75% to about 99% identical to that of Gene ID: 64895, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 64895. In some embodiments, a *PAPOLG* variant is a *PAPOLG* polynucleotide that exhibits at least one polymorphism in the *PAPOLG* coding region as compared to the coding
5 region of Gene ID: 64895. In some embodiments, a *PAPOLG* variant is associated with a favorable response to treatment, such as vedolizumab.

An individual who is heterozygous or homozygous for a *PAPOLG* variant is “*PAPOLG* variant positive.”

As used herein, “*SLC47A1*” refers to the Solute Carrier Family 47 (Multidrug And Toxin
10 Extrusion), Member 1 gene, which is located on chromosome 17. The start and end positions are located at 19,432,166 and 19,487,346. An exemplary gene sequence is Gene ID: 55244.

As used herein, “*SLC47A1* variant” is a *SLC47A1* gene with a sequence identity that is less than 100% identical to that of Gene ID: 55244. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 55244, such
15 as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of Gene ID: 55244. In some embodiments, a *SLC47A1* variant is a *SLC47A1* polynucleotide that exhibits at least one polymorphism in the *SLC47A1* coding region as compared to the coding region of Gene ID: 55244. In some embodiments, a *SLC47A1* variant is associated with a favorable response to treatment, such as vedolizumab.

20 An individual who is heterozygous or homozygous for a *SLC47A1* variant is “*SLC47A1* variant positive.”

As used herein, “*WRAP53*” refers to the WD Repeat Containing, Antisense to TP53 gene, which is located on chromosome 17. The start and end positions are located at 7,584,388 and 7,611,820. An exemplary gene sequence is Gene ID: 55135.

25 As used herein, “*WRAP53* variant” is a *WRAP53* gene with a sequence identity that is less than 100% identical to that of Gene ID: 55135. In some embodiments, the variant has a sequence identity that is from about 75% to about 99% identical to that of Gene ID: 55135, such as about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% identical to that of

Gene ID: 55135. In some embodiments, a *WRAP53* variant is a *WRAP53* polynucleotide that exhibits at least one polymorphism in the *WRAP53* coding region as compared to the coding region of Gene ID: 55135. In some embodiments, a *WRAP53* variant is associated with a favorable response to treatment, such as vedolizumab.

5 An individual who is heterozygous or homozygous for a *WRAP53* variant is “*WRAP53* variant positive.”

As used herein, the term “variant” may refer to a “single nucleotide polymorphism” or “SNP”. In particular, the term “variant” may refer to the SNPs specifically disclosed herein.

As used herein, a single nucleotide polymorphism is a variation at a single position in a
10 DNA sequence among individuals. For example, if more than 1% of a population does not carry the same nucleotide at a specific position in the DNA sequence, then this variation can be classified as a SNP. If a SNP occurs within a gene, then the gene is described as having more than one allele. In these cases, SNPs may lead to variations in the amino acid sequence. SNPs, however, are not just associated with genes; they can also occur in noncoding regions of DNA.

15 Although a particular SNP may not cause a disorder, some SNPs can be associated with certain diseases. These associations may allow the determination of one or more SNPs in order to evaluate an individual's genetic predisposition to develop a disease. In addition, if certain SNPs are known to be associated with a trait, stretches of DNA near these SNPs may be examined in an attempt to identify the gene or genes responsible for the trait.

20 Known SNPs can be taken from databases such as the SNP database at the NCBI (National Center for Biotechnology Information, Bethesda, MD; available at ncbi.nlm.nih.gov/SNP).

The SNPs as described herein may be present on the Watson or the Crick strand, with presence of the corresponding base. If, for example, a polymorphism is present on the Watson
25 strand as A, it is present on the Crick strand as T, if the polymorphism is present on the Watson strand as T, it is present on the Crick strand as A, if the polymorphism is present on the Watson strand as G, it is present on the Crick strand as C, and if the polymorphism is present on the Watson strand as C, it is present on the Crick strand as G, and *vice versa*. Also, the insertion or

deletion of bases may be detected on the Watson and/or the Crick strand, with correspondence as defined above. For analytic purposes the strand identity may be defined, or fixed, or may be chosen at will, e.g. in dependence on factors such the availability of binding elements, GC-content etc. Furthermore, for the sake of accuracy, the SNP may be defined on both strands
5 (Crick and Watson) at the same time, and accordingly be analyzed.

The term "allele" or "allelic sequence" as used herein refers to a particular form of a gene or a particular nucleotide, e.g. a DNA sequence at a specific chromosomal location or locus. In certain embodiments a SNP as defined herein may be found at or on one of two alleles in the human genome of a single subject. In further specific embodiments, a SNP as defined herein
10 may also be found at or on both alleles in the human genome of a single subject. The presence of an indicator nucleotide or an indicator triplet as defined herein on both alleles may have a higher predictive value than the presence of an indicator nucleotide or an indicator triplet on one allele only, the other allele comprising a wild-type genotype.

The nucleotide that is present in the majority of the population is also referred to as wild-
15 type allele or major allele. In one embodiment, the term "wild-type sequence" as used herein refers to the sequence of an allele, which is not predictive for the subject's treatment response to a $\alpha 4\beta 7$ integrin antagonist. In another embodiment, the term "wild-type sequence" as used herein refers to the sequence of an allele, which is predictive for the subject's treatment response to a $\alpha 4\beta 7$ integrin antagonist. The term may further refer to the sequence of the non phenotype-associated allele with the highest prevalence within a population, e.g. within a Caucasian
20 population. As used herein, this state is defined as "absence of a SNP".

The specific nucleotide that is present in the minority of the population is also referred as the point mutation, mutated nucleotide or minor allele. As used herein, this state is defined as "presence of a SNP", "the presence of a polymorphic variant" or "the presence of a biomarker".

25 In theory, the wild-type allele could be mutated to three different nucleotides. However, the event of a mutation to a first nucleotide in the reproductive cells of an individual that gets established in a population occurs very rarely. The event that the same position is mutated to a second nucleotide and established in the population virtually never occurs and can be therefore

neglected. Therefore, as used herein, a certain nucleotide position in the genome of an individual can have two states, the wild-type state (absence of a SNP) and the mutated state (presence of a SNP).

As described above, the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* gene in a sample of a patient can be indicative for a treatment response to a $\alpha 4\beta 7$ integrin antagonist. The at least one polymorphic variant in the *TRABD2B* gene may be selected from a group of biomarkers. The term "biomarker", as used herein, relates to any nucleic acid sequence of any length, or a derivative thereof, which comprises a polymorphic variant such as the polymorphic variant in the genes described herein. In particular, the term "biomarker" may relate to SNPs.

The term "indicator nucleotide" may refer to a non-wild-type nucleotide at positions of the sequences as described in Tables 1B and 7 and SEQ ID NOs. 1-25.

Both the presence and the absence of an indicator nucleotide, i.e. a single nucleotide polymorphism, can be predictive for a patient's response to treatment. This is also reflected in the embodiments described herein.

Polymorphisms in linkage disequilibrium with a SNP as disclosed herein can be identified by methods known in the art. For example, Develin and Risch (1995) Genomics: 29(2): 311-322 provide guidance for determining the parameter delta (also referred to as the "r") as a standard measure of the disequilibrium. Gabriel *et al.* (2002) Science 296(5576):2225-2229 provides instructions for finding the maximal r^2 value in populations for disease gene mapping. Further, Carlson *et al.* (2004) Am. J. Hum. Genet. 74(1): 106-120 disclose methods for selecting and analyzing polymorphisms based on linkage disequilibrium for disease gene association mapping. Stoyanovich and Pe'er (2008) Bioinformatics 24(3): 440-442 show that polymorphisms in linkage disequilibrium with identified SNPs have virtually identical response profiles. Currently, several databases provide datasets that can be searched for polymorphisms in strong linkage disequilibrium, which can be accessed at the websites maintained by the following entities : 1000 Genomes project website maintained by the European Bioinformatics Institute, Hinxton, Cambridge, UK the International HapMap Project (website maintained by NCBI), the

SNAP (SNP Annotation and Proxy Search website maintained by the Broad Institute, Cambridge MA. An example workflow for determining SNPs linkage disequilibrium to a specific SNP is outlined in Uhr *et al.* (2008) Neuron 57(2): 203-209.

As used herein, a SNP in strong linkage disequilibrium with a SNP as specified herein may refer
5 to a SNP that is in linkage disequilibrium with an r^2 equal to or higher than 0.8, preferably equal to or higher than 0.9 and most preferably equal to or higher than 0.95 in the tested population or an ethnically close reference population with the specified SNP.

Methods of Treatment

“Treatment” as used herein refers to any measure that imparts a benefit to a subject
10 afflicted with or diagnosed with Crohn’s Disease (*i.e.*, an enhanced treatment effect), including improvement in the condition of the subject, *e.g.*, human, or in one or more symptoms of Crohn’s Disease. In some embodiments, the improvement comprises clinical remission (*e.g.*, as determined by a Crohn’s Disease Activity Index (CDAI) score of ≤ 150 points at week 2, 4, 6, and/or 10 of treatment), and/or an enhanced clinical response (*e.g.*, as determined by a ≥ 100
15 point decrease in CDAI score from baseline). In some embodiments, treatment includes remission of the underlying condition and/or symptoms thereof. “Treatment” does not necessarily imply that the subject will be treated until total recovery. As used herein, a “favorable” response or that a patient will “respond favorably” to treatment with an $\alpha 4\beta 7$ antagonist for the treatment of Crohn’s disease is that the patient will have clinical response
20 and/or clinical remission of the disease, by typical clinical measures. For example, clinical response is a 70 point or greater decrease in the Crohn’s Disease Activity Index (CDAI) score from the baseline at entering treatment.

The term “treatment response” is intended to mean that a subject which is characterized by the presence or absence of at least one SNP as discussed herein shows an improvement in the
25 condition of the subject or in one or more symptoms of Crohn’s disease as described above.

The term "subject eligible for treatment with a $\alpha 4\beta 7$ antagonist" as used herein may refer to a patient with inflammatory bowel disease, for example Crohn’s disease, who shows, or is

predicted to show, a positive treatment response during and/or after the treatment with said $\alpha 4\beta 7$ antagonist compared to the state before the treatment. In one embodiment, a subject eligible for treatment with a $\alpha 4\beta 7$ antagonist is identified by the methods for predicting a treatment response to an $\alpha 4\beta 7$ antagonist as described herein.

5 As used herein, an “ $\alpha 4\beta 7$ antagonist” is a molecule which antagonizes, reduces or inhibits the function of $\alpha 4\beta 7$ integrin. Such antagonist may antagonize the interaction of $\alpha 4\beta 7$ integrin with one or more of its ligands. Human $\alpha 4\beta 7$ integrin is a heterodimer of an $\alpha 4$ chain (CD49D, ITGA4) and a $\beta 7$ chain (ITGB7). Each chain can form a heterodimer with an alternative integrin chain, to form $\alpha 4\beta 1$ or $\alpha E\beta 7$. Human $\alpha 4$ and $\beta 7$ genes (GenBank (National Center for
10 Biotechnology Information, Bethesda, MD) RefSeq Accession numbers NM_000885 and NM_000889, respectively) are expressed by B and T lymphocytes, particularly memory CD4+ lymphocytes. Ligands for $\alpha 4\beta 7$ integrin include vascular cell adhesion molecule (VCAM), fibronectin and mucosal addressin (MAdCAM (e.g., MAdCAM-1)).

An $\alpha 4\beta 7$ antagonist may bind either chain of the heterodimer or a complex requiring both
15 chains of the $\alpha 4\beta 7$ integrin, or it may bind a ligand, such as MAdCAM. An $\alpha 4\beta 7$ antagonist may be an antibody which performs such binding function, such as an anti- $\alpha 4\beta 7$ -integrin antibody (e.g., MLN0002, described in PCT publications nos. WO98/06248 and WO07/61679, vedolizumab Chemical Abstract Service (CAS, American Chemical Society) Registry number 943609-66-3, or AMG-181 or other antibodies described in US 2010/0254975); an anti- $\alpha 4$ -
20 integrin antibody (e.g., humanized MAb 21.6 (Bendig *et al.*, U.S. Pat. No. 5,840,299) and derivatives thereof), an anti- $\beta 7$ -integrin antibody (e.g., FIB504 or a humanized derivative (e.g., Fong *et al.*, U.S. Pat. No. 7,528,236), an anti-MAdCAM antibody (see e.g., US Patent No. 8,277,808, PF-00547659 or antibodies described in WO2005/067620), or an engineered form of a ligand, such as a MAdCAM-Fc chimera such as described in US Patent No. 7,803,904. In
25 some embodiments, an $\alpha 4\beta 7$ antagonist has “binding specificity for the $\alpha 4\beta 7$ complex” and binds to $\alpha 4\beta 7$, but not to $\alpha 4\beta 1$ or $\alpha E\beta 7$. Treatment methods using anti- $\alpha 4\beta 7$ integrin antibodies are described in publication nos. U.S. 2005/0095238, U.S. 2005/0095238, WO2012151248 and WO 2012/151247.

In some embodiments, the methods comprise treating Crohn's Disease in an individual identified as *TRABD2B* variant positive, *CLDN7* variant positive, *GABARAP* variant positive, *ELP5* variant positive, *CTDNEP1* variant positive, *PDC* variant positive, *DLG4* variant positive, *MIR324* variant positive, *ONECUT1* variant positive, and/or *NPY* variant positive. In some
5 embodiments, the methods comprise treating Crohn's Disease in an individual identified as *C5orf20* variant positive, *CLN5* variant positive, *COL24A1* variant positive, *TIFAB* variant positive, *PLAGL1* variant positive, *CEP72* variant positive, *FBXL3* variant positive, *PAPOLG* variant positive, *SLC47A1* variant positive, and/or *WRAP53* variant positive.

In some embodiments, the methods comprise treating Crohn's Disease in an individual
10 identified as (i) *TRABD2B* variant positive, (ii) *PDC* variant positive, (iii) *NPY* variant positive, (iv) *ONECUT1* variant positive, (v) *DLG4* variant positive, (vi) *CLDN7* variant positive, (vii) *ELP5* variant positive, or (viii) any combination of these as provided herein by administering an anti- $\alpha 4\beta 7$ antibody to the individual. In some embodiments, the individual is *TRABD2B* variant positive, *PDC* variant positive, *NPY* variant positive, *ONECUT1* variant positive, *DLG4* variant
15 positive, *CLDN7* variant positive, and *ELP5* variant positive. In some embodiments, the anti- $\alpha 4\beta 7$ antibody is vedolizumab.

In some embodiments, methods for treating Crohn's Disease in an individual comprises determining that the individual is *TRABD2B* variant positive, *CLDN7* variant positive, *GABARAP* variant positive, *ELP5* variant positive, *CTDNEP1* variant positive, *PDC* variant
20 positive, *DLG4* variant positive, *MIR324* variant positive, *ONECUT1* variant positive, *NPY* variant positive, or any combination of these, and administering to the individual an $\alpha 4\beta 7$ integrin antagonist, such as a treatment selected from the group consisting of vedolizumab, natalizumab, etrolizumab, AMG181 and $\alpha 4\beta 7$ ligand (MAdCAM-1) binding agents such as PF-547659 or other monoclonal antibodies or small molecules that target the same mechanism of
25 action.

In some embodiments, methods for treating Crohn's Disease in an individual comprises determining that the individual is *C5orf20* variant positive, *CLN5* variant positive, *COL24A1* variant positive, *TIFAB* variant positive, *PLAGL1* variant positive, *CEP72* variant positive,

FBXL3 variant positive, *PAPOLG* variant positive, *SLC47A1* variant positive, *WRAP53* variant positive, or any combination of these, and administering to the individual vedolizumab, natalizumab, etrolizumab, AMG181 and/or $\alpha 4\beta 7$ ligand (MAdCAM-1) binding agents such as PF-547659 or other monoclonal antibodies or small molecules that target the same mechanism of action.

In some embodiments, methods for treating Crohn's Disease in an individual comprises determining that the individual is (i) *TRABD2B* variant positive, (ii) *PDC* variant positive, (iii) *NPY* variant positive, (iv) *ONECUT1* variant positive, (v) *DLG4* variant positive, (vi) *CLDN7* variant positive, (vii) *ELP5* variant positive, or (viii) any combination of these, such as *TRABD2B*, *PDC*, *NPY*, *ONECUT1*, *DLG4*, *CLDN7*, and *ELP5* variant positive and administering to the individual vedolizumab, natalizumab, etrolizumab, AMG181 and/or $\alpha 4\beta 7$ ligand (MAdCAM-1) binding agents such as PF-547659 or other monoclonal antibodies or small molecules that target the same mechanism of action.

Vedolizumab may be administered by any suitable method, such as by one or more of intravenous injection, subcutaneous injection, or infusion. In some embodiments, vedolizumab is administered at a dose of 50 mg, 100 mg, 300 mg, or 500 mg. In some embodiments, the vedolizumab is administered, for example subcutaneously, at a dose of 0.05 mg/kg, 0.10 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.4 mg/kg, or 0.5 mg/kg, at a dose of 108 mg, 216 mg, 160 mg or 165 mg. The vedolizumab may be administered once per day, per week, per month, or per year. In some embodiments, the vedolizumab is administered at zero, two and six weeks, and then every four weeks or every eight weeks thereafter. In some embodiments, vedolizumab is administered one or more times, and then at least one month, at least six months, or at least one year later, vedolizumab is again administered one or more times. In some embodiments, 300 mg vedolizumab may be administered by intravenous infusion at zero, two, and six weeks, and then at four weeks intervals or eight week intervals thereafter. In some embodiments, 300 mg vedolizumab may be administered by intravenous infusion at zero, two, and six weeks, and then at two, three or four weeks intervals, 108 mg of vedolizumab may be administered subcutaneously.

In some embodiments, methods comprise determining the likelihood that an individual suffering from Crohn's disease is likely to experience an enhanced treatment effect when treated with vedolizumab. In some embodiments, the methods comprise assaying a biological sample obtained from an individual for the presence or absence of a *TRABD2B* variant, a *CLDN7* variant, a *GABARAP* variant, an *ELP5* variant, a *CTDNEP1* variant, a *PDC* variant, a *DLG4* variant, a *MIR324* variant, a *ONECUT1* variant, and/or a *NPY* variant. In some embodiments, the methods comprise assaying a biological sample obtained from an individual for the presence or absence of a *C5orf20* variant, a *CLN5* variant, a *COL24A1* variant, a *TIFAB* variant, a *PLAGL1* variant, a *CEP72* variant, a *FBXL3* variant, a *PAPOLG* variant, a *SLC47A1* variant, and/or a *WRAP53* variant. In some embodiments, the methods comprise assaying a biological sample obtained from an individual for the presence or absence of a *TRABD2B* variant and/or a *PDC* variant and/or a *NPY* variant and/or a *ONECUT1* variant and/or a *DLG4* variant and/or a *CLDN7* variant and/or a *ELP5* variant and (ii) detecting the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.

In some embodiments, the individual is determined to experience an enhanced treatment effect when treated with vedolizumab if the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant are present in nucleic acids from the individual.

In some embodiments, the methods comprise administering vedolizumab to the individual that is *TRABD2B* variant positive, *PDC* variant positive, *NPY* variant positive, *ONECUT1* variant positive, *DLG4* variant positive, *CLDN7* variant positive, and/or *ELP5* variant positive.

Some embodiments comprise the use of an active agent in the treatment of Crohn's Disease in an individual. Some embodiments comprise an active agent for use as a medicament in the treatment of Crohn's Disease in an individual. Some embodiments comprise use of an active agent in the preparation of a medicament for the treatment of Crohn's Disease in an individual. In some embodiments, the individual is identified as or characterized as being (i)

TRABD2B variant positive, (ii) *PDC* variant positive, (iii) *NPY* variant positive, (iv) *ONECUT1* variant positive, (v) *DLG4* variant positive, (vi) *CLDN7* variant positive, (vii) *ELP5* variant positive, or (viii) any combination of these as provided herein by administering an anti- $\alpha 4\beta 7$ antibody to the individual. In some embodiments, the individual is *TRABD2B* variant positive, *PDC* variant positive, *NPY* variant positive, *ONECUT1* variant positive, *DLG4* variant positive, *CLDN7* variant positive, and *ELP5* variant positive. In some embodiments, the active agent is an anti-integrin antibody selected from the group consisting of vedolizumab, natalizumab, etrolizumab, and AMG181, or an anti- $\alpha 4\beta 7$ ligand antibody (such as an antibody that binds MAdCAM-1) including binding agents such as PF-547659.

One aspect of the invention comprises an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been selected for treatment with said antagonist by having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample obtained from said subject, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject is selected for treatment with said $\alpha 4\beta 7$ integrin antagonist by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample obtained from said subject, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample obtained from said subject, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been identified as being eligible for treatment with said $\alpha 4\beta 7$ integrin antagonist by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject is selected for said treatment by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with inflammatory bowel disease, wherein the subject has been selected by determining or having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

Some embodiments comprise an $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with inflammatory bowel disease, wherein the subject is characterized by the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus and the treatment comprises a step of determining whether the single nucleotide polymorphism in the *TRABD2B* genomic locus is present or absent, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is associated with a response to said treatment.

In some embodiments, the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

In the above embodiments, the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus can be selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

5 In one embodiment, the presence or absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is or has been determined, wherein for example the absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

10 In another embodiment, the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573 is or has been determined wherein for example the absence of the single nucleotide polymorphisms rs6671927, rs2088361 and rs1556981 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably, the subject is or has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist by using the following formula:

$$15 \text{ } Score_i = (0.32 * rs1561573) - (0.4502 * rs6671927) - (0.6524 * rs2088361) - (0.8948 * rs1556981),$$

wherein the value for rs1561573, rs6671927, rs2088361 and rs1556981, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present
20 and wherein a subject having a score of more than -1.4350 is or has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

In another embodiment the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573 is or has been determined, wherein for example the absence of the single nucleotide polymorphisms rs6671927, rs2088361,
25 rs1556981 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably, the subject is or has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist by using the following formula:

$$Score_i = (0.2738 * rs1561573) - (0.3913 * rs6671927) - (0.5404 * rs2088361) - (0.7396 * rs1556981) - (0.1912 * rs11205430),$$

wherein the value for rs1561573, rs6671927, rs2088361, rs1556981 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.3896 is or has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

In still another embodiment the presence or absence of the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, and rs11211632 is or has been determined, wherein for example the absence of the single nucleotide polymorphisms rs11211613, rs12061891, rs11211632 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably, the subject is or has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:

$$Score_i = (0.2865 * rs1561573) - (0.3678 * rs11211613) - (1.0079 * rs12061891) - (0.5831 * rs11211632) - (0.2351 * rs11205430),$$

wherein the value for rs1561573, rs11211613, rs12061891, rs11211632 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, of more than -1.5910 is or has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

In addition to determining the presence or absence of at least one single nucleotide polymorphism in the TRABD2B genomic locus, the presence or absence of at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* may have been determined.

Preferably, the presence or absence of at least one single nucleotide polymorphism in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* is or has been determined.

For example, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926 and rs11801527.

For example, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141 and rs3779477.

For example, the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750 and rs7180600.

5 For example, the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408 and rs1875673.

For example, the single nucleotide polymorphism in the *ELP5* genomic locus is rs2106842.

10 Preferably, the presence or absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842 is or has been determined. More preferably, the absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842 is predictive for the subject's treatment response to said
15 $\alpha 4\beta 7$ integrin antagonist. Even more preferably, the subject is or has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist by using the following formula:

$$Score_i = (-0.1797 * rs7543124) - (0.3707 * rs6671927) - (0.5741 * rs2088361) - (0.5848 * rs1556981) + (0.7127 * rs1882926) - (0.7024 * rs11801527) - (0.6841 * rs3779477) + (0.2158 * rs2440335) + (0.6147 * rs1899750) + (0.3475 * rs1875673) + (0.397 * rs2106842),$$

20 wherein the value for rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.2123 is or has been selected for treatment with said $\alpha 4\beta 7$
25 integrin antagonist.

Preferably, the presence or absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 is or has been determined. More preferably, the absence of the single nucleotide polymorphisms

rs7543124, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs1899750 and rs2106842 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist. Even more preferably, the subject is or has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:

$$Score_i = (-0.2213 * rs7543124) - (0.8735 * rs2088361) - (0.659 * rs1556981) + (0.8567 * rs1882926) - (0.858 * rs11801527) - (0.6935 * rs3779477) + (0.9288 * rs1899750) + (0.7159 * rs2106842)$$

wherein the value for rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.6803 is or has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

Methods of Predicting Response to Vedolizumab

Methods for determining the likelihood that an individual suffering from Crohn's disease will respond favorably to treatment with an anti-integrin antibody (e.g., vedolizumab, natalizumab, etrolizumab, or AMG181) or an anti- $\alpha 4\beta 7$ ligand antibody (e.g., an antibody that binds MAdCAM-1) including binding agents such as PF-547659 are also provided herein. In some embodiments, the method comprises assaying and/or analyzing a sample from the individual to determine the presence of absence of a *TRABD2B* variant, a *CLDN7* variant, a *GABARAP* variant, an *ELP5* variant, a *CTDNEP1* variant, a *PDC* variant, a *DLG4* variant, a *MIR324* variant, a *ONECUT1* variant, and/or a *NPY* variant, and determining that the individual is likely to respond favorably to treatment when the individual possesses the *TRABD2B* variant, the *CLDN7* variant, the *GABARAP* variant, the *ELP5* variant, the *CTDNEP1* variant, the *PDC* variant, the *DLG4* variant, the *MIR324* variant, the *ONECUT1* variant, and/or the *NPY* variant. In some embodiments, the method comprises assaying and/or analyzing a sample from the individual to determine the presence of absence of a *C5orf20* variant, a *CLN5* variant, a *COL24A1* variant, a *TIFAB* variant, a *PLAGL1* variant, a *CEP72* variant, a *FBXL3* variant, a

PAPOLG variant, a *SLC47A1* variant, and/or a *WRAP53* variant, and determining that the individual is likely to respond favorably to treatment when the individual possesses the *C5orf20* variant, the *CLN5* variant, the *COL24A1* variant, the *TIFAB* variant, the *PLAGL1* variant, the *CEP72* variant, the *FBXL3* variant, the *PAPOLG* variant, the *SLC47A1* variant, and/or the *WRAP53* variant. In some embodiments, the assay is performed *in vitro*. The sample can be assayed and/or analyzed before, during, and/or after the individual begins treatment for Crohn's disease. In some embodiments, the sample is obtained prior to treatment with the $\alpha 4\beta 7$ integrin antagonist, such as vedolizumab. In some embodiments, the sample is obtained after the first dose of the $\alpha 4\beta 7$ integrin antagonist, such as vedolizumab. In some embodiments, the sample is obtained after two doses of the $\alpha 4\beta 7$ integrin antagonist, such as vedolizumab. In some embodiments, the sample is obtained during the sixth week of treatment with the $\alpha 4\beta 7$ integrin antagonist, such as vedolizumab. In some embodiments, the methods comprise recording and/or transmitting the result of the assay and/or analysis. In some embodiments, the methods comprise authorizing payment for treatment and/or paying for the treatment.

In some embodiments, the methods comprise assaying and/or analyzing a sample from the individual to determine the presence of absence of a *TRABD2B* variant and/or a *PDC* variant and/or *NPY* variant positive and/or a *ONECUT1* variant and/or a *DLG4* variant and/or a *CLDN7* variant and/or a *ELP5* variant in nucleic acids from the individual, and determining that the individual is likely to respond favorably to treatment with vedolizumab when the individual possesses a *TRABD2B* variant and/or a *PDC* variant and or a *NPY* variant and/or a *ONECUT1* variant and/or a *DLG4* variant and/or a *CLDN7* variant and/or a *ELP5* variant.

The present invention also relates to a method for predicting a treatment response to an $\alpha 4\beta 7$ integrin antagonist in a subject with Crohn's disease, said method comprising the step of determining the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a nucleic acid sample obtained from said subject, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

Preferably, the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

As used herein, “predicting a treatment response” means that based on the result of the analysis of at least one single nucleotide polymorphism as disclosed herein a subject is considered to be likely to respond to the treatment with a $\alpha 4\beta 7$ integrin antagonist.

Accuracy, sensitivity, precision, specificity and negative predictive value are exemplary
5 statistical measures of the performance of the prediction method. In the following, examples are given for determining the performance of the prediction methods described herein.

As used herein, accuracy may be calculated as (number of true positives + number of true negatives) / (number of true positives + number of false positives + number of true negatives +
10 number of false negatives), e.g. (number of patients correctly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist + number of patients correctly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist) / (number of patients correctly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist + number of patients wrongly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist + number of patients correctly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist + number of patients wrongly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist). The accuracy of prediction
15 may e.g. be at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 90 to 99% or 95 to 99%.

As used herein, sensitivity may be calculated as (true positives) / (true positives + false negatives), e.g.: (number of patients correctly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist) / (number of patients correctly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist +
20 number of patients wrongly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist). The sensitivity of prediction may be at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 90 to 99% or 95 to 99%.

As used herein, precision (also referred to as positive predictive value) may be calculated as (true positives) / (true positives + false positives), e.g.: (number of patients correctly
25 diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist) / (number of patients correctly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist + number of patients wrongly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist). The precision of prediction may be at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 90 to 99% or 95 to 99%.

As used herein, specificity is calculated as (true negatives) / (true negatives + false positives), e.g.: (number of patients correctly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist) / (number of patients correctly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist + number of patients wrongly diagnosed as responding to $\alpha 4\beta 7$ integrin antagonist).

5 The specificity of prediction may be at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 90 to 99% or 95 to 99%.

As used herein, negative predictive value is calculated as (true negatives) / (true negatives + false negatives), e.g.: (number of patients correctly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist) / (number of patients correctly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist + number of patients wrongly diagnosed as not responding to $\alpha 4\beta 7$ integrin antagonist). The negative predictive value may be at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 90 to 99% or 95 to 99%.

Other statistical measures useful for describing the performance of the prediction methods described herein include geometric mean of sensitivity and specificity, geometric mean of positive predictive value and negative predictive value, F-measure and area under ROC curve, and the positive and negative likelihood ratios, the false discovery rate and Matthews correlation coefficient. These measures and method for their determination are well known in the art.

For a prediction whether a patient is likely to respond to the treatment with a $\alpha 4\beta 7$ integrin antagonist the prediction method described herein may include determining a number of SNPs and/or combinations of SNPs sufficient to achieve a prediction sensitivity and/or precision of at least 55%, optionally at least 80%.

For the prediction whether it is unlikely that a patient responds to the treatment with a $\alpha 4\beta 7$ integrin antagonist the prediction method described herein may include determining a number of SNPs and/or combinations of SNPs sufficient to achieve a prediction specificity and/or negative predictive value of at least 55%, optionally at least 80%.

For a prediction whether a patient responds to a treatment with $\alpha 4\beta 7$ integrin antagonists or not the prediction method described herein may include determining a number of SNPs and/or

combinations of SNPs sufficient to achieve sensitivity and/or precision and/or specificity and/or negative predictive value of at least 55%, optionally at least 80%.

In exemplary embodiments, the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

In exemplary embodiments, the presence or absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is determined, wherein for example the absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

In another embodiment, the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573 can be determined, wherein for example the absence of the single nucleotide polymorphisms rs6671927, rs2088361 and rs1556981 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist. In an exemplary embodiment, a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (0.32 * rs1561573) - (0.4502 * rs6671927) - (0.6524 * rs2088361) - (0.8948 * rs1556981),$$

wherein the value for rs1561573, rs6671927, rs2088361 and rs1556981, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.4350 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

In another embodiment, the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573 can be determined, wherein for example the absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive

for the treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably, a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (0.2738 * rs1561573) - (0.3913 * rs6671927) - (0.5404 * rs2088361) - (0.7396 * rs1556981) - (0.1912 * rs11205430),$$

5 wherein the value for rs1561573, rs6671927, rs2088361, rs1556981 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.3896 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

10 In another embodiment, the presence or absence of the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632 can be determined, wherein for example the absence of the single nucleotide polymorphisms rs11211613, rs12061891, rs11211632 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably, a subject that
15 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:
$$Score_i = (0.2865 * rs1561573) - (0.3678 * rs11211613) - (1.0079 * rs12061891) - (0.5831 * rs11211632) - (0.2351 * rs11205430),$$

wherein the value for rs1561573, rs11211613, rs12061891, rs11211632 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single
20 nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.5910 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

In exemplary embodiments, the presence or absence of at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*,
25 *ONECUT1*, *DLG4* and *ELP5* can additionally be determined.

In exemplary embodiments, the presence or absence of at least one single nucleotide polymorphism in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* is determined.

In an exemplary embodiment, the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926 and rs11801527, the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141 and rs3779477, the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of, rs2440335, rs2440332, rs1899750 and rs7180600, the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408 and rs1875673 and/or the single nucleotide polymorphism in the *ELP5* genomic locus is rs2106842.

In a specific embodiment, the presence or absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842 can be determined, wherein for example the absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (-0.1797 * rs7543124) - (0.3707 * rs6671927) - (0.5741 * rs2088361) - (0.5848 * rs1556981) + (0.7127 * rs1882926) - (0.7024 * rs11801527) - (0.6841 * rs3779477) + (0.2158 * rs2440335) + (0.6147 * rs1899750) + (0.3475 * rs1875673) + (0.397 * rs2106842),$$

wherein the value for rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.2123 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

In another embodiment the presence or absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 can be determined, wherein for example the absence of the single nucleotide

polymorphisms rs7543124, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs1899750 and rs2106842 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist. Preferably, a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (-0.2213 * rs7543124) - (0.8735 * rs2088361) - (0.659 * rs1556981) + (0.8567 * rs1882926) - (0.858 * rs11801527) - (0.6935 * rs3779477) + (0.9288 * rs1899750) + (0.7159 * rs2106842)$$

wherein the value for rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.6803 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy. In some embodiments, determining whether an individual is *TRABD2B* variant positive, *PDC* variant positive, *NPY* variant positive, *ONECUT1* variant positive, *DLG4* variant positive, *CLDN7* variant positive, and/or *ELP5* variant positive or predicting a treatment response to an $\alpha 4\beta 7$ integrin antagonist as discussed above involves obtaining a biological sample from an individual.

A sample, e.g., a biological sample, can be any substance that contains nucleic acids from the individual, such as a body fluid sample, a tissue sample, a stool sample, cells from the individual, and/or isolated nucleic acids from the individual. Exemplary body fluid samples include blood, plasma, serum, cerebrospinal fluid, bile and saliva. Exemplary tissue samples include tissue biopsy samples, such as an intestinal biopsy sample (e.g., from colon tissue or ileum tissue). Exemplary cell samples include buccal swabs or cells obtained from biological samples taken from the individual. Methods of extracting nucleic acids from samples are well known in the art and can be readily adapted to obtain a sample that is compatible with the system utilized. In some embodiments, the samples are enriched and/or stabilized. In some embodiments, the samples are centrifuged through Ficoll. Automated sample preparation systems for extracting nucleic acids from a test sample are commercially available, e.g., Roche Molecular Systems' (Pleasanton, CA, USA) COBAS AmpliPrep System, Qiagen's (Venlo,

Netherlands) BioRobot 9600, and Applied Biosystems' (Watham, MA, USA) PRISM™ 6700 sample preparation system.

As used herein, “isolated nucleic acids” means nucleic acid that is removed to at least some extent from the cellular material from which they originated. However, “isolated” does not
5 require that the nucleic acid be completely pure and free of any other components. Examples of isolated nucleic acid are those obtained using commercial nucleic extraction kits.

In some embodiments, a sample from an individual contains DNA and/or RNA from the individual. In some embodiments, assaying a sample involves extracting nucleic acids from a biological sample to determine that the individual is positive for any of the variants described
10 herein. For example, some embodiments comprise extracting nucleic acids from a biological sample to determine that the individual is *TRABD2B* variant positive and/or *PDC* variant positive and/or *NPY* variant positive and/or *ONECUT1* variant positive and/or *DLG4* variant positive and/or *CLDN7* variant positive and/or *ELP5* variant positive. Various methods of extraction are suitable for isolating DNA or RNA. Suitable methods include phenol and chloroform extraction.
15 See Maniatis et al., Molecular Cloning, A Laboratory Manual, 2d, Cold Spring Harbor Laboratory Press, page 16.54 (1989). Numerous commercial kits also yield DNA and/or RNA. However, nucleic acid extraction is not essential and a sample, such as blood or saliva, may be assayed directly to determine that the individual is *TRABD2B* variant positive and/or *PDC* variant positive and/or *NPY* variant positive and/or *ONECUT1* variant positive and/or *DLG4*
20 variant positive and/or *CLDN7* variant positive and/or *ELP5* variant positive without extracting nucleic acids from the sample.

In some embodiments, assaying a sample comprises reverse transcribing RNA to produce cDNA.

In some embodiments, assaying a sample comprises amplifying nucleic acids in the
25 sample or nucleic acids derived from nucleic acids in the sample (e.g. cDNA). Amplification methods which may be used include variations of RT-PCR, including quantitative RT-PCR, for example as adapted to the method described by Wang, A. M. et al., Proc. Natl. Acad. Sci. USA 86:9717-9721, (1989), or by Karet, F. E., et al., Analytical Biochemistry 220:384-390, (1994).

Another method of nucleic acid amplification or mutation detection which may be used is ligase chain reaction (LCR), as described by Wiedmann, et al., PCR Methods Appl. 3:551-564, (1994). An alternative method of amplification or mutation detection is allele specific PCR (ASPCR). ASPCR which utilizes matching or mismatching between the template and the 3' end base of a primer well known in the art. *See e.g.*, U.S. Pat. No. 5,639,611, which is incorporated herein by reference and made a part hereof.

In some embodiments, the methods comprise determining the presence of a genetic variant with nucleic acid sequencing. Sequencing can be performed using any number of methods, kits or systems known in the art. One example is using dye terminator chemistry and an ABI sequencer (Applied Biosystems, Foster City, Calif.). Sequencing also may involve single base determination methods such as single nucleotide primer extension ("SNaPshot® " sequencing method) or allele or mutation specific PCR. The SNaPshot® Multiplex System is a primer extension-based method that enables multiplexing up to 10 SNPs (single nucleotide polymorphisms). The chemistry is based on the dideoxy single-base extension of an unlabeled oligonucleotide primer (or primers). Each primer binds to a complementary template in the presence of fluorescently labeled ddNTPs and AmpliTaq® DNA Polymerase, FS. The polymerase extends the primer by one nucleotide, adding a single ddNTP to its 3' end. SNaPshot® Multiplex System is commercially available (ABI PRISM. SNaPshot® Multiplex kit, Applied Biosystems Foster City, Calif.). Products generated using the ABI PRISM® SNaPshot® Multiplex kit can be analyzed with GeneScan® Analysis Software version 3.1 or higher using ABI PRISM® 310 Genetic Analyzer, ABI PRISM® 3100 Genetic Analyzer or ABI PRISM® 3700 DNA Analyzer.

A person skilled in the art will recognize that, based on the SNP and associated sequence information disclosed herein, detection reagents can be developed and used to assay any SNP of the present technology individually or in combination, and that such detection reagents can be incorporated into a kit.

The term "kit" as used herein in the context of SNP detection reagents, refers to such things as combinations of multiple SNP detection reagents, or one or more SNP detection

reagents in combination with one or more other types of elements or components (*e.g.*, other types of biochemical reagents, containers, packages such as packaging intended for commercial sale, substrates to which SNP detection reagents are attached, electronic hardware components, *etc.*).

5 Accordingly, the present technology further provides SNP detection kits and systems, including but not limited to, packaged probe and primer sets (*e.g.*, TaqMan probe/primer sets), arrays/microarrays of nucleic acid molecules, and beads that contain one or more probes, primers, or other detection reagents for detecting one or more SNPs described herein. The kits can optionally include various electronic hardware components. For example, arrays ("DNA
10 chips") and microfluidic systems ("lab-on-a-chip" systems) provided by various manufacturers typically comprise hardware components. Some kits (*e.g.*, TaqMan probe/primer sets) may not include electronic hardware components, but may be comprised of, for example, one or more SNP detection reagents (along with other optional biochemical reagents) packaged in one or more containers.

15 In some embodiments, a SNP detection kit contains one or more detection reagents and other components (*e.g.*, buffers, reagents, enzymes having polymerase activity, enzymes having polymerase activity and lacking 5'→3' exonuclease activity or both 5'→3' and 3'→5' exonuclease activity, ligases, enzyme cofactors such as magnesium or manganese, salts, chain extension nucleotides such as deoxynucleoside triphosphates (dNTPs) or biotinylated dNTPs, and in the
20 case of Sanger-type DNA sequencing reactions, chain terminating nucleotides (*i.e.*, dideoxynucleoside triphosphates (ddNTPs), positive control sequences, negative control sequences, and the like) to carry out an assay or reaction, such as amplification and/or detection of a SNP-containing nucleic acid molecule. In some embodiments, a kit contains a means for determining the amount of a target nucleic acid, determining whether an individual is
25 heterozygous or homozygous for a polymorphism, detecting a gene transcript, and/or comparing the amount with a standard. In some embodiments, the kit comprises instructions for using the kit to detect the SNP-containing nucleic acid molecule of interest. In some embodiments, the kits contain reagents to carry out one or more assays to detect one or more SNPs disclosed

herein. In some embodiments, SNP detection kits are in the form of nucleic acid arrays or compartmentalized kits, including microfluidic/lab-on-a-chip systems.

The kits may further comprise one or more of: wash buffers and/or reagents, hybridization buffers and/or reagents, labeling buffers and/or reagents, and detection means. The buffers and/or reagents can be optimized for the particular amplification/detection technique for which the kit is intended. Protocols for using these buffers and reagents for performing different steps of the procedure may also be included in the kit.

In some embodiments, the SNP detection kits comprise at least one set of primers (*e.g.*, comprising one matched allele-specific primer and one mismatched allele-specific primer) and, optionally, a non-extendable oligonucleotide probe. Each kit can comprise reagents which render the procedure specific. Thus, a kit intended to be used for the detection of a particular SNP can comprise a matched and mismatched allele-specific primers set specific for the detection of that particular SNP, and optionally, a non-extendable oligonucleotide probe. A kit intended to be used for the multiplex detection of a plurality of SNPs comprises a plurality of primer sets, each set specific for the detection of one particular SNP, and, optionally, a plurality of corresponding non-extendable oligonucleotide probes.

In some embodiments, the SNP detection kits comprise multiple pairs of primers for one or more target SNP loci, wherein said primers are designed so that the lengths of said PCR products from different SNP loci or from different alleles of the same SNP locus are sufficiently distinguishable from each other in capillary electrophoresis analysis, thus making them suitable to multiplex PCR. The SNP detection kit can further comprise a fluorescently labeled single-base extension/termination reagent, *i.e.*, ddNTPs, to label the primers during the multiplex PCR reaction (*e.g.*, SNaPshot Multiplex). The chemistry of the SNP detection kit can be based on the dideoxy single-base extension of the unlabeled primers. Each primer can bind to its target SNP loci in the presence of fluorescently labeled ddNTPs and the polymerase extends the primer by one nucleotide, adding a single ddNTP to its 3' end. The identity of the incorporated nucleotide can be determined by the fluorescence color readout. In some embodiments, the kits comprise multiple pairs of primers for simultaneously detecting at least one SNP locus having two or more

different alleles. In some embodiments, the kits comprise multiple pairs of primers for simultaneously detecting different genotypes among 1-8 different SNP loci. In some embodiments, the SNP detection kit comprises multiple pairs of primers that have the annealing temperatures designed to be used in a single amplification reaction. In some embodiments, the kits further comprise an internal control polynucleotide and/or multiple control primers for conducting multiplex PCR using the internal control polynucleotide as a template.

In some embodiments, SNP detection kits may contain, for example, one or more probes, or pairs of probes, that hybridize to a nucleic acid molecule at or near each target SNP position. Multiple pairs of allele-specific probes may be included in the kit to simultaneously assay multiple SNPs, at least one of which is a SNP disclosed herein. In certain embodiments, multiple pairs of allele-specific probes are included in the kit to simultaneously assay all of the SNPs described herein. In some embodiments, the kit includes capture primers and optionally extension primers for the detection of one or a plurality of SNPs of one or more genes selected from the group consisting of *TRABD2B*, *PDC*, *NPY*, *ONECUT1*, *DLG4*, *CLDN7*, *ELP5*, *GABARAP*, *CTDNEP1*, *MIR324*, *C5orf20*, *CLN5*, *COL24A1*, *TIFAB*, *PLAGL1*, *CEP72*, *FBXL3*, *PAPOLG*, *SCL47A1*, and *WRAP53*.

In some embodiments, the SNP detection kits comprise at least one set of pre-selected nucleic acid sequences that act as capture probes for the extension products. The pre-selected nucleic acid sequences (allele-specific probes) may be immobilized on an array or beads (e.g., coded beads), and can be used to detect at least 1, 4, 10, 11, all, or any combination of the SNPs disclosed herein. By way of example only, the kits may include polystyrene microspheres that are internally dyed with two spectrally distinct fluorescent dyes (e.g., x-MAP™ microbeads, Luminex Corp. (Austin, Tex.)). Using precise ratios of these fluorophores, a large number of different fluorescent bead sets can be produced (e.g., a set of 100). Each set of beads can be distinguished by its code (or spectral signature) and can be used to detect a large number of different extension products in a single reaction vessel. These sets of fluorescent beads with distinguishable codes can be used to label extension products. Labeling (or attachment) of extension products to beads can be by any suitable means including, but not limited to, chemical

or affinity capture, cross-linking, electrostatic attachment, and the like. In some embodiments, labeling of extension products is carried out through hybridization of the allele-specific primers and the tag probe sequences. The magnitude of the biomolecular interaction that occurs at the microsphere surface is measured using a third fluorochrome that acts as a reporter (*e.g.*,
5 biotinylated dNTPs). Because each of the different extension products is uniquely labeled with a fluorescent bead, the captured extension product (indicative of one allele of a SNP of interest) can be distinguishable from other different extension products (including extension products indicative of other alleles of the same SNP and extension products indicative of other SNPs of interest). Following hybridization, the microbeads can be analyzed using methods such as flow
10 cytometry. In embodiments where the primer extension reaction is carried out in the presence of biotinylated dNTPs, the reaction between beads and extension products may be quantified by fluorescence after reaction with fluorescently-labeled streptavidin (*e.g.*, Cy5-streptavidin conjugate) using instruments such as the Luminex® 100™ Total System, Luminex® 100™ IS Total System, Luminex™ High Throughput Screening System).

15 Some embodiments provide methods of identifying the SNPs disclosed herein in a biological sample comprising incubating a test sample of nucleic acids obtained from the subject with an array comprising one or more probes corresponding to at least one SNP position disclosed herein, and assaying for binding of a nucleic acid from the test sample with one or more of the probes. Conditions for incubating a test sample with a SNP detection reagent from a
20 kit that employs one or more such SNP detection reagents can vary. Incubation conditions depend on factors such as the format employed in the assay, the detection methods employed, and the type and nature of the detection reagents used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification and array assay formats can readily be adapted to detect the SNPs disclosed herein.

25 In some embodiments, the SNP detection kits of the present technology include control analytes for spiking into a sample, buffers, including binding, washing and elution buffers, solid supports, such as beads, protein A or G or avidin coated sepharose or agarose, *etc.*, and a matrix-assisted laser desorption/ionization (MALDI) sample plate. The kit may also contain a database,

which may be a table, on paper or in electronic media, containing information for one or a plurality of SNPs of one or more genes selected from the group consisting of *TRABD2B*, *PDC*, *NPY*, *ONECUT1*, *DLG4*, *CLDN7*, *ELP5*, *GABARAP*, *CTDNEP1*, *MIR324*, *C5orf20*, *CLN5*, *COL24A1*, *TIFAB*, *PLAGL1*, *CEP72*, *FBXL3*, *PAPOLG*, *SLC47A1*, and *WRAP53*. In some
5 embodiments, the kits contain programming to allow a robotic system to perform the present methods, *e.g.*, programming for instructing a robotic pipettor or a contact or inkjet printer to add, mix and remove reagents. The various components of the kit may be present in separate containers or certain compatible components may be precombined into a single container, as desired.

10 In some embodiments, the kits include one or more other reagents for preparing or processing an analyte sample for matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). The reagents may include one or more matrices, solvents, sample preparation reagents, buffers, desalting reagents, enzymatic reagents, denaturing reagents, where calibration standards such as positive and negative controls may be provided as well. As such,
15 the kits may include one or more containers such as vials or bottles, with each container containing a separate component for carrying out a sample processing or preparing step and/or for carrying out one or more steps of a MALDI-TOF protocol.

In addition to above-mentioned components, the kits can include instructions for using the components of the kit, *e.g.*, to prepare a MALDI-TOF sample plate and/or assess a sample.
20 The instructions, such as for preparing or assessing a sample *via* MALDI-TOF, are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, *etc.* As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (*i.e.*, associated with the packaging or subpackaging) *etc.* In some embodiments, the instructions are present as
25 an electronic storage data file present on a suitable computer readable storage medium. In some embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, *e.g. via* the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or

from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate. In addition to the database, programming and instructions, the kits may also include one or more control analyte mixtures, *e.g.*, two or more control samples for use in testing the kit.

5 Sequencing can be performed using any number of methods, kits or systems known in the art. One example is using dye terminator chemistry and an ABI sequencer (Applied Biosystems, Foster City, Calif.). Sequencing also may involve single base determination methods such as single nucleotide primer extension ("SNaPshot® " sequencing method) or allele or mutation specific PCR. The SNaPshot® Multiplex System is a primer extension-based method that
10 enables multiplexing up to 10 SNPs (single nucleotide polymorphisms). The chemistry is based on the dideoxy single-base extension of an unlabeled oligonucleotide primer (or primers). Each primer binds to a complementary template in the presence of fluorescently labeled ddNTPs and AmpliTaq® DNA Polymerase, FS. The polymerase extends the primer by one nucleotide, adding a single ddNTP to its 3' end. SNaPshot® Multiplex System is commercially available
15 (ABI PRISM. SNaPshot® Multiplex kit, Applied Biosystems Foster City, Calif.). Products generated using the ABI PRISM® SNaPshot® Multiplex kit can be analyzed with GeneScan® Analysis Software version 3.1 or higher using ABI PRISM® 310 Genetic Analyzer, ABI PRISM® 3100 Genetic Analyzer or ABI PRISM® 3700 DNA Analyzer.

Next generation sequencing (NGS) may be used to determine an individual's genotype.
20 Next generation sequencing is a high throughput, massively parallel sequencing method that can generate multiple sequencing reactions of clonally amplified molecules and of single nucleic acid molecules in parallel. This allows increased throughput and yield of data. NGS methods include, for example, sequencing-by-synthesis using reversible dye terminators, and sequencing-by-ligation. Non-limiting examples of commonly used NGS platforms include
25 Miseq/Nextseq/HiSeq (Illumina, Inc.), Roche 454™ GS FLX™-Titanium (Roche Diagnostics), XMAP® (Luminex Corp.), IONTORRENT™ (Life Technologies Corp.) and ABI SOLiD™ System (Applied Biosystems, Foster City, CA).

Some embodiments as described herein are directed to kits comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant as described herein, and (ii) a detectably labeled probe that hybridizes to the genetic variant. In some embodiments, the kits comprise at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939, rs6684538, rs1882926, rs11801527, rs12407957, rs10798041, rs16141, rs3779477, rs16129, rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, rs2106842, exm1286317, rs2074217, and rs222843.

Some embodiments are directed to kits comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs1556981, rs2088361, rs1561573, and rs6671927, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

Some embodiments are directed to kits comprising: a pair of primers that specifically hybridizes to rs1556981; a pair of primers that specifically hybridizes to rs2088361; a pair of primers that specifically hybridizes to rs1561573; and a pair of primers that specifically hybridizes to rs6671927.

Some embodiments are directed to kits comprising: a pair of primers that specifically hybridizes to rs1556981; a pair of primers that specifically hybridizes to rs2088361; a pair of primers that specifically hybridizes to rs1561573; a pair of primers that specifically hybridizes to rs6671927; and a pair of primers that specifically hybridizes to rs11205430.

Some embodiments are directed to kits comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs1561573, rs11211613, rs12061891, rs11211632, and rs11205430, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

Some embodiments are directed to kits comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of

rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

Some embodiments are directed to kits comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of
5 rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

EXAMPLES

Example 1 – Identification of SNPs Associated with Clinical Remission or Enhanced Clinical Response

Whole genome genotyping data on 1,390 samples from two clinical trials (C13007 and C13011) was assayed for 964,193 variants using an Illumina HumanOmniExpressExome Beadchip array. Genotypic quality control was performed using per-sample and per-variant quality control procedures, which narrowed the raw dataset of 1,390 samples and 964,193
15 variants to 1,365 samples and 811,254 variants. See Figure 1A. Baseline characteristics of the patients are shown in Figure 1B.

Following quality control, the top 10 gene regions associated with clinical remission or enhanced clinical response at a 6-week endpoint were identified using a region test-based linear mixed model framework. The top 10 genes associated with clinical remission are shown in
20 Figures 2A-D, where Figure 2A shows results in all patients; Figure 2B shows results from clinical trial C13007; Figure 2C shows results from clinical trial C13011; and Figure 2D shows results in all Caucasian patients. The top 10 genes associated with enhanced clinical response are shown in Figures 3A-D, where Figure 3A shows results in all patients; Figure 3B shows results in clinical trial C13007; Figure 3C shows results in clinical trial C13011; and Figure 3D
25 shows results in all Caucasian patients.

Association Testing of Genomic Features

The following types of genomic features based on genetic variants (e.g. single nucleotide polymorphisms, i.e. SNPs; insertions; or deletions) were considered in the present study: (i) A SNP with Minor Allele Frequency (MAF) $\geq 5\%$; and (ii) a gene of interest, which was defined as the region between the transcription start and end positions plus 5kb upstream and downstream of the transcription start and end positions.

For all single variant analyses, a genotypic or dominant model was considered for variants that passed genotypic QC. Specifically, the following genetic models were used to accommodate single variant analyses: (a) A genotypic model (i.e. a model with $g-1$ degrees of freedom (d.f.), where g = the number of observed genotypes) was considered for common variants (i.e. MAF $\geq 5\%$) with genotype counts of at least 5 for all genotype categories; and (ii) a dominant model (i.e. a model with 1 d.f., where presence vs. absence of the minor allele was modeled) was used for common variants with less than 5 observations for any of the genotypes. A variant was omitted from single variant testing if the variant had less than 5 observations in the heterozygous and rare homozygous groups combined. For multi-variant analyses, each variant was coded as the number of minor alleles (i.e. 0, 1, or 2).

A tiered approach was employed to prioritize the genomic regions of interest in association testing. Tier 1 genomic regions were defined in part as genes/SNPs residing in regions covered by the Immunochip.

A two-stage approach was utilized to identify genes or single variants predictive of response to Vedolizumab treatment in clinical remission at week 6 in trials C13007 and C13011.

In Stage 1, the effect of genetic variation (SNP or gene) on clinical remission at week 6 was assessed in patients treated by Vedolizumab or placebo in trials C13007 and C13011. Single variants or genes with an unadjusted P-value < 0.1 were carried forward into the second stage.

In stage 2, the interaction between genetic variation (SNP or gene) and the treatment (i.e. Vedolizumab vs. placebo) was assessed on clinical remission at week 6 using samples treated by Vedolizumab or placebo in trials C13007 and C13011. Multiplicity adjustment was considered by tier.

A flexible regression framework was considered for gene-level association testing or single variant association testing. For the stage 1 analysis, the following logistic regression model was considered for testing gene/SNP main effect on clinical remission at week 6:

$$\text{logit}(\pi(\mathbf{X}_i, \mathbf{B}_i, T_i)) = \mathbf{X}_i^T \boldsymbol{\alpha} + T_i \beta_T + f(\mathbf{B}_i) \quad (1)$$

where π denotes the probability of response, $\mathbf{X}_i$ and $\mathbf{B}_i$ were the i th subject's covariate vector and biomarker vector, T_i denotes an indicator variable for treatment assignment for subject i (i.e. $T_i=1$ if Vedolizumab treated), and $\boldsymbol{\alpha}$ was the coefficient vector for the covariate vector. The top 3 Principal Components derived from a Principal Component Analysis as well as a baseline CDAI score, prior treatment, geographic region, treatment were included in the model as covariates.

For the stage 2 analysis, the following interaction model was considered for clinical remission:

$$\text{logit}(\pi(\mathbf{X}_i, \mathbf{B}_i, T_i)) = \mathbf{X}_i^T \boldsymbol{\alpha} + T_i \beta_T + f(\mathbf{B}_i) + T_i * f(\mathbf{B}_i) \quad (2)$$

The biomarker vector $\mathbf{B}_i$ was a general placeholder that represented the corresponding biomarker.

Subgroup Identification

Subgroup identification was considered for the primary endpoint week 6 clinical remission. A subgroup $\mathcal{S}$ was assumed to exhibit enhanced treatment effect of Vedolizumab as compared to placebo. The problem of subgroup identification was written in the logistic regression framework as

$$\text{logit}(\pi(\mathbf{X}_i, \mathbf{G}_i)) = \mathbf{X}_i^T \boldsymbol{\alpha}_0 + \mathbf{G}_i^T \boldsymbol{\alpha}_1 + T_i \beta_T + T_i \beta_S \cdot I(i \in \mathcal{S})$$

where β_S denoted enhanced treatment effect in a subgroup $\mathcal{S}$ that was added to the treatment main effect. Since true subgroup membership cannot be observed, biomarkers were used as surrogates to infer subgroup membership.

A multi-marker composite score approach was used in the development of a genetic signature that could be used to infer subgroup membership. A subgroup was identified using a

two-stage approach: Stage 1: Develop a composite score using a subset of biomarkers (i.e. genetic variants) via a penalized regression approach; and Stage 2: Find a composite score cutoff that defines a subgroup. The composite score was derived by fitting a working model

$$\logit(\pi(X_i, G_i)) = X_i^T \alpha_0 + B_i^T \alpha_1 + T_i \beta_T + T_i B_i^T \theta$$

where $T_i B_i^T \theta$ contained interaction terms of the treatment T_i with each biomarker.

The composite score was then defined as $y = B_i^T \theta$, in which increasing values of the composite score would be indicative of a benefit (i.e., increasing Odds Ratio). The model above was fit using the elastic net (Zou and Hastie, *J. R. Statist. Soc. B*, 67: 301-320 (2005)), which performed feature selection through penalized regression. For biomarkers that did not contribute significantly to the composite score, the corresponding parameter estimates could be shrunk to zero in the composite score calculation and subsequently only biomarkers with non-zero parameter estimates were used in the definition of a genetic signature.

A subgroup of patients was defined using the estimated composite scores $\{\hat{y}_i; i = 1, \dots, n\}$ for n patients. Given a threshold of $\tau \in \{\tau = 1, \dots, n; T_i = 1\}$, the subgroup was defined as $S_\tau = \{i : \hat{y}_i \geq \tau, i = 1, \dots, n\}$. To choose the optimal value $\tau = \tau_*$ and the corresponding subgroup S_{τ_*} , a grid search was used to consider all possible τ 's in the designated range of 25-75% and to choose the optimal value $\tau = \tau_*$ maximizing a χ^2 -test statistic. To account for the multiple testing performed when searching for the optimal threshold, significance of the treatment-by-subgroup interaction at the optimal cutoff was evaluated using a parametric bootstrap approach.

Example 2 – 19 SNP Model

Common variants located in the top 10 genes identified in the Genome-Wide Association Study were employed to build a second model for subgroup identification. After genotypic QC, 90 common variants located in the top 10 genes were identified. LD pruning was performed to eliminate high-LD structures among the SNPs (r^2 threshold = 0.8). 59 out of the 90 variants

survived LD-pruning and were selected as candidate variants for constructing genetic composite scores in subgroup identification. A penalized regression approach (Zou and Hastie, 2005) was employed to select the 19 SNPs set forth in Table 1.

5 Table 1A. 19 SNPs Selected by Penalized Regression from the Top 10 Genes

SNP ID	Gene	Chr	Position	Allele	MAF f	β	$2f(1-f) \beta^2$
rs7543124	TRABD2B	1	48227135	A/G	0.3421	-0.0328	5e-04
rs6671927	TRABD2B	1	48285768	C/T	0.3023	-0.2116	0.0189
rs12134443	TRABD2B	1	48286563	T/C	0.2725	0.0947	0.0036
rs11211624	TRABD2B	1	48359634	G/T	0.1436	-0.2432	0.0145
rs2088361	TRABD2B	1	48362713	G/A	0.4136	-0.203	0.02
rs1556981	TRABD2B	1	48370525	T/C	0.1736	-0.0591	0.001
rs11205430	TRABD2B	1	48442182	A/G	0.3729	-0.1212	0.0069
rs1882926	PDC	1	186411579	A/C	0.1293	0.3725	0.0312
rs11801527	PDC	1	186418798	A/G	0.1324	-0.2811	0.0182
rs16141	NPY	7	24324759	A/C	0.4927	0.1875	0.0176
rs3779477	NPY	7	24327526	T/C	0.4399	-0.3734	0.0687
rs2440335	ONECUT1	15	53046210	G/A	0.4396	0.0583	0.0017
rs2440332	ONECUT1	15	53050252	T/C	0.2828	0.1976	0.0158
rs1899750	ONECUT1	15	53068506	C/T	0.3923	0.1935	0.0179
rs7180600	ONECUT1	15	53070141	A/G	0.1575	-0.0116	<1e-04
rs17203281	DLG4	17	7099811	A/G	0.3234	-0.0485	0.001
rs3826408	DLG4	17	7101292	T/C	0.4663	-0.1688	0.0142
rs1875673	DLG4	17	7108506	T/G	0.3201	0.2052	0.0183
rs2106842	CLDN7, ELP5	17	7162451	G/A	0.3692	0.2324	0.0252

Table 1B: 19-SNP Model – Flanking Sequences

SNP ID	Gene	Flanking Sequence	SEQ ID No.
rs7543124	TRABD2B	GGCAGCAGTCAAGCCCAGCTGGGTC[A/G]TTG AAGGGGGCGCTGTGAGGGGTGG	1
rs6671927	TRABD2B	ACACACTATGTTAGTTCTCACTTA[C/T]CATGT TTATTGTTTATCACATCACC	2
rs12134443	TRABD2B	TTCAGTTTTTAAAATAATAAGACTA[C/T]GGCT CAGAGAGGCTGAACAAGTTGC	3
rs11211624	TRABD2B	CTGGCATTATCCCGAAACCCCAAA[G/T]AACC TGCTGTGGATCCTCCCTCTGA	4
rs2088361	TRABD2B	TTGCTATGTTTTTTGTTTACTGTCC[A/G]TCTTA CCCTATCACATCCAATACCT	5
rs1556981	TRABD2B	TTCTCACTCTGCTTTCAAAATATAA[C/T]ATCCT CTGTGCTCTCTCCCGATATA	6
rs11205430	TRABD2B	CATAGTAGGTGCTAAGAATACAGAC[A/G]ACA CACAAATATTTCTACTCTCATG	7
rs1882926	PDC	CTTTAGATATCTCTTTTGAGAGACA[A/C]AATT GTAAAGGAAAGAGAAGTGAGT	14
rs11801527	PDC	TAAAGTATTTAGAATGTTTCTGTCC[A/G]CAAT GTAAAAGGACATTAATTTAAC	15
rs16141	NPY	CCCGCGCTCCTCCTCCTGCTACCAC[A/C]CGCG ACCCCAATCCGCTCTCGTCC	16
rs3779477	NPY	TTAAAAACACACTCTAAAGCCCAGG[C/T]CCCA TCCCAGAGGGTCTGATTTAAT	17
rs2440335	ONECUT1	CCTGTAGAGGGGAGGGAGTTGTGAC[A/G]TCTG GACACCCCAAAACCCCAGACT	18
rs2440332	ONECUT1	AAATACTCATCAAAGCCACAACCCA[C/T]GCCC AGGCCTCACAGAACTTCACCT	19
rs1899750	ONECUT1	TGACATCCACATAACCACTCTGCAG[C/T]TAAA GGTATATCCAAGCACCCAGCT	20
rs7180600	ONECUT1	TCCTCCCGTCCAAAAATGGCTGAAT[A/G]TAAT TCCTATGAGAGCTGATATTTA	21
rs17203281	DLG4	TGGTACCTTCTGGTTTATACTGAGC[A/G]ATGA TCGTGACCGTCTGACCCGCAT	22
rs3826408	DLG4	AGGTAGCGCTACGTTCTTCCTACAG[C/T]ATCA CCACAGGATGCAATAATGCCT	23
rs1875673	DLG4	ACGCAGTGCAAAGGACGTCAGGAAC[A/G/T]GG GAGTGGTGAAAGACATCCGGGTC	24
rs2106842	CLDN7, ELP5	TCTTTTCTCTCCCTTATACCCTTGG[A/G]TCACA GCTCCAGTTGTCCCCAGAGC	25

Table 1A shows genes and gene combinations whose genotypes can be combined in multigene models that significantly correlate with clinical remission in adult patients treated with vedolizumab, and Table 1B shows flanking sequences (based on dbSNP from NCBI) for the SNPs in the multigene model. The 19-variant (19-SNP) model shows statistically significant evidence for a treatment-specific effect. A subgroup identified via the genetic signature set forth in Figure 4 showed statistically significant enhanced treatment effect in adult Crohn's Disease patients treated with vedolizumab. See Figure 4, where the left markings for vedolizumab and placebo represent patients "not in the subgroup" and the right markings in each category represent patients "in the subgroup." Moreover, the subjects outside the subgroup showed a significant non-response effect. See Figure 4. The distribution of a Biomarker+ subgroup (in the subgroup) and a Biomarker- subgroup (not in the subgroup) in vedolizumab- and placebo-treated CD patients is shown in Table 2. The subgroup showing enhanced treatment effect was identified using a parametric bootstrapping approach, similar to that set forth in Li et al., "A multi-marker molecular signature approach for treatment-specific subgroup identification with survival outcomes," The Pharmacogenomics Journal, 14(5): 439-45 (2014), which is incorporated herein by reference and made a part hereof. In particular, the dataset was bootstrapped multiple times, and each bootstrapped dataset was used to re-estimate a score using elastic net. Using this approach, a coefficient for each SNP was estimated. Using these coefficients, for each signature, the patient's score is calculated as:

$$Score_i = \sum_j G_j \beta_j$$

where j indicates the j th SNP, and the patient's membership is

$$Membership_i = \begin{cases} 1, & \text{if } Score_i \geq \text{threshold} \\ 0, & \text{if } Score_i < \text{threshold} \end{cases}$$

In the equation, G is 0, 1, or 2, depending on the number of patient's minor allele and coefficient β is selected for each particular variant. Using this equation, responders were identified using the following formula, where the optimal cutoff was $\tau_* = 0.1102$:

$$\begin{aligned}
Score_i = & (rs7543124 \text{ coefficient}) * rs7543124 + (rs6671927 \text{ coefficient}) * rs6671927 + \\
& (rs12134443 \text{ coefficient}) * rs12134443 + (rs11211624 \text{ coefficient}) * rs11211624 + (rs2088361 \\
& \text{coefficient}) * rs2088361 + (rs1556981 \text{ coefficient}) * rs1556981 + (rs11205430 \text{ coefficient}) * \\
& rs11205430 + (rs1882926 \text{ coefficient}) * rs1882926 + (rs11801527 \text{ coefficient}) * rs11801527 + \\
& (rs16141 \text{ coefficient}) * rs16141 + (rs3779477 \text{ coefficient}) * rs3779477 + (rs2440335 \text{ coefficient}) \\
& * rs2440335 + (rs2440332 \text{ coefficient}) * rs2440332 + (rs1899750 \text{ coefficient}) * rs1899750 + \\
& (rs7180600 \text{ coefficient}) * rs7180600 + (rs17203281 \text{ coefficient}) * rs17203281 + (rs3826408 \\
& \text{coefficient}) * rs3826408 + (rs1875673 \text{ coefficient}) * rs1875673 + (rs2106842 \text{ coefficient}) * \\
& rs2106842.
\end{aligned}$$

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Table 2: Distribution of biomarker+ subgroup (in the subgroup) and biomarker-subgroup (Not in the subgroup) CD patients in the 19-SNP model.

Treatment	In the Subgroup	Not in the Subgroup
Vedolizumab	132 (38.82%)	208 (61.18%)
Placebo	92 (33.58%)	182 (66.42%)
Total	224 (36.48%)	390 (63.52%)

15 *Example 3 – 11 SNP Model*

The 19-SNP model was refined to construct an 11-SNP model. Table 3 shows genes and gene combinations whose expression levels can be combined in multigene models that significantly correlate with clinical remission in adult Crohn's Disease patients treated with vedolizumab.

Table 3: 11 variants used in genetic signature

SNP ID	Gene	MAF f	β	$2f(1-f)\beta^2$
rs7543124	TRABD2B	0.3421	-0.1797	0.0145
rs6671927	TRABD2B	0.3023	-0.3707	0.058
rs2088361	TRABD2B	0.4136	-0.5741	0.1599
rs1556981	TRABD2B	0.1736	-0.5848	0.0981
rs1882926	PDC	0.1293	0.7127	0.1144
rs11801527	PDC	0.1324	-0.7024	0.1134
rs3779477	NPY	0.4399	-0.6841	0.2306
rs2440335	ONECUT1	0.4396	0.2158	0.0229
rs1899750	ONECUT1	0.3923	0.6147	0.1801
rs1875673	DLG4	0.3201	0.3475	0.0526
rs2106842	CLDN7, ELP5	0.3692	0.397	0.0734

The 11-variant (11-SNP) model shows statistically significant evidence for a treatment-specific effect. A subgroup identified via the genetic signature in Table 3 showed a statistically significant clinical remission treatment effect. See Figure 5A, where the left markings for vedolizumab and placebo represent patients “not in the subgroup,” the middle markings in each category represent the “treatment main effect,” and the right markings in each category represent patients “in the subgroup.” Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 5A. The subgroup showing enhanced treatment effect was identified using the parametric bootstrapping methods set forth in Example 2. In particular, responders were identified using the following formula, where the optimal cutoff was $\tau_* = 0.2123$:

$$Score_i = (\text{rs7543124 coefficient}) * \text{rs7543124} + (\text{rs6671927 coefficient}) * \text{rs6671927} + (\text{rs2088361 coefficient}) * \text{rs2088361} + (\text{rs1556981 coefficient}) * \text{rs1556981} + (\text{rs1882926 coefficient}) * \text{rs1882926} + (\text{rs11801527 coefficient}) * \text{rs11801527} + (\text{rs3779477 coefficient}) * \text{rs3779477} + (\text{rs2440335 coefficient}) * \text{rs2440335} + (\text{rs1899750 coefficient}) * \text{rs1899750} + (\text{rs1875673 coefficient}) * \text{rs1875673} + (\text{rs2106842 coefficient}) * \text{rs2106842}.$$

The specific algorithm used was as follows:

$$\begin{aligned} \text{Score}_i = & -0.1797 * \text{rs7543124} - 0.3707 * \text{rs6671927} - 0.5741 * \text{rs2088361} - 0.5848 * \\ & \text{rs1556981} + 0.7127 * \text{rs1882926} - 0.7024 * \text{rs11801527} - 0.6841 * \text{rs3779477} + 0.2158 * \\ & \text{rs2440335} + 0.6147 * \text{rs1899750} + 0.3475 * \text{rs1875673} + 0.397 * \text{rs2106842}, \end{aligned}$$

5

where the value for rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842, respectively, is 0, 1, or 2, depending on the number of the patient's minor allele.

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The distribution of Biomarker+ subgroup (In the subgroup) and Biomarker– subgroup (not in the subgroup) in vedolizumab- and placebo-treated CD patients is shown in Table 4.

Table 4: Distribution of Biomarker+ subgroup (in the subgroup) and Biomarker– subgroup (Not in the subgroup) CD patients in the 11-SNP model

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	Not in subgroup (%)	In subgroup (%)	Total
Placebo	198 (72.26)	76 (27.74)	274
Vedolizumab	235 (69.12)	105 (30.88)	340
Total	433 (70.52)	181 (29.48)	614

Figures 5B and 5C show clinical remission over time during the induction phase in the C13007 and C13011 trials, respectively.

Figure 5D shows a statistically significant enhanced clinical response treatment effect.

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See Figure 5D, where the left markings for vedolizumab and placebo represent patients “not in the subgroup,” the middle markings in each category represent the overall “treatment main effect” and the right markings in each category represent patients “in the subgroup.” Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 5D. Figure 5E and 5F show enhanced clinical response over time in the C13007 and C13011

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trials, respectively.

Figure 5G shows plots of CDAI scores versus genetic biomarker scores for both vedolizumab treatment and placebo treatment in the 11-SNP model. Figure 5H shows observed vs. predicted CDAI scores for the 11-SNP model.

5 *Example 4 – 8 SNP Model*

The 19-SNP model was refined to construct an 8-SNP model. Table 5 shows genes and gene combinations whose genotypes can be combined in multigene models that significantly correlate with clinical remission in adult Crohn's Disease patients treated with vedolizumab.

Table 5: 8 variants used in genetic signature

SNP ID	Gene	MAF f	β	$2f(1-f)\beta^2$
rs7543124	TRABD2B	0.3421	-0.2213	0.022
rs2088361	TRABD2B	0.4136	-0.8735	0.3701
rs1556981	TRABD2B	0.1736	-0.659	0.1246
rs1882926	PDC	0.1293	0.8567	0.1653
rs11801527	PDC	0.1324	-0.858	0.1692
rs3779477	NPY	0.4399	-0.6935	0.237
rs1899750	ONECUT1	0.3923	0.9288	0.4113
rs2106842	CLDN7, ELP5	0.3692	0.7159	0.2387

The 8-variant (8-SNP) model shows statistically significant evidence for a treatment-specific effect. A subgroup identified via the genetic signature in Table 5 showed a statistically significant clinical remission treatment effect. See Figure 6, where the left markings for vedolizumab and placebo represent patients “not in the subgroup” and the right markings in each category represent patients “in the subgroup.” Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 6. The subgroup showing enhanced treatment effect was identified using the parametric bootstrapping methods set forth in Example 2. In particular, responders were identified using the following formula, where the optimal cutoff was $\tau_* = 0.6803$:

$$Score_i = (\text{rs7543124 coefficient}) * \text{rs7543124} + (\text{rs2088361 coefficient}) * \text{rs2088361} + (\text{rs1556981 coefficient}) * \text{rs1556981} + (\text{rs1882926 coefficient}) * \text{rs1882926} + (\text{rs11801527 coefficient}) * \text{rs11801527} + (\text{rs3779477 coefficient}) * \text{rs3779477} + (\text{rs1899750 coefficient}) * \text{rs1899750} + (\text{rs2106842 coefficient}) * \text{rs2106842}.$$

The specific algorithm used was as follows:

$$Score_i = -0.2213 * \text{rs7543124} - 0.8735 * \text{rs2088361} - 0.659 * \text{rs1556981} + 0.8567 * \text{rs1882926} - 0.858 * \text{rs11801527} - 0.6935 * \text{rs3779477} + 0.9288 * \text{rs1899750} + 0.7159 * \text{rs2106842},$$

where the value for rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs1899750, and rs2106842, respectively, is 0, 1, or 2, depending on the number of the patient's minor allele.

The distribution of Biomarker+ subgroup (In the subgroup) and Biomarker- subgroup (not in the subgroup) in vedolizumab- and placebo-treated CD patients is shown in Table 6.

Table 6: Distribution of Biomarker+ subgroup (in the subgroup) and Biomarker- subgroup (Not in the subgroup) CD patients in the 8-SNP model

	In the Subgroup	Not in the Subgroup
Vedolizumab	82 (24.12%)	258 (75.88%)
Placebo	62 (22.63%)	212 (77.37%)
Total	144 (23.45%)	470 (76.55%)

Example 5 – 4 SNP Model

Common variants located in the TRABD2B gene were of interest for subgroup identification based on association testing results. 45 common variants located in this gene passed genotypic QC. A penalized regression approach (Zou and Hastie, 2005) was employed to
5 select the 13 SNPs set forth in Table 7. The 13-SNP model was found to significantly identify a responder subgroup.

Table 7. SNPs Selected by Penalized Regression from TRABD2B

SNP ID	Chromosome	Position	MAF	Allele	Flanking sequence	SEQ ID No.
rs7543124	1	48227135	0.3421	A/G	GGCAGCAGTCAAGCCCAGCTGGGTC [A/G]TTGAAGGGGGCGCTGTGAGGG GTGG	1
rs1561573	1	48227943	0.4833	C/T	GTGGCTGGTCAGCAGGGTTGGGTCA [C/T]GAAGGGTCTAGCGGACACTTC AGGG	8
rs6671927	1	48285768	0.3023	C/T	ACACACTATGTTAGTTCCTCACTTA[C/T]CATGTTTATTGTTTATCACATCA CC	2
rs12134443	1	48286563	0.2725	T/C	TTCAGTTTTTAAAATAATAAGACTA[C/T]GGCTCAGAGAGGCTGAACAAGT TGC	3
rs11211613	1	48290860	0.307	A/C	AAGCTCTTCCAAATCTGGGGTCTCA[A/C]TAATTCTCACAATAGCCATTTTG CA	9
rs11211624	1	48359634	0.1436	G/T	CTGGCATTATCCCGAAACCCCAAA [G/T]AACCTGCTGTGGATCCTCCCTC TGA	4
rs2088361	1	48362713	0.4136	G/A	TTGCTATGTTTTTTGTTTACTGTCC[A /G]TCTTACCCTATCACATCCAATACC T	5
rs1556981	1	48370525	0.1736	T/C	TTCTCACTCTGCTTTCAAAATATAA[C/T]ATCCTCTGTGCTCTCTCCCGATA TA	6
rs6684538	1	48380390	0.4425	A/G	CTCCATAGAAAGAGCTGGTCCATTG [A/G]CACTGCTCAGAAGGCCTGAGT CAGC	13
rs12061891	1	48392033	0.1454	C/T	CGTTCTATTGCACTGTAGATCTGCC[C/T]GGGCCAAGTCATGGCTCCTGGG GGC	10
rs11211632	1	48406460	0.441	A/G	GGATGCAGGAATAAAAATAAGCTTC [A/G]GCCAGAGAGAAATAAAGGCAG CAGT	11
rs17103939	1	48409812	0.1465	C/T	GAATAAAGGATGATGCTGCAGGAC A[C/T]GGGAGTGCATGAGCCCAGGA ATGGA	12
rs11205430	1	48442182	0.3729	A/G	CATAGTAGGTGCTAAGAATACAGAC [A/G]ACACACAAATATTTCTACTCTC ATG	7

6 SNPs were removed from these 13 SNPs to eliminate high LD structure using an r^2 threshold of 0.8: rs11211613, rs11211624, rs6684538, rs12061891, rs11211632, and rs17103939. A model refinement approach was then applied to the 7 remaining SNPs, and 4 SNPs were selected to construct a final model based on model performance.

These 4 SNPs (Table 8) significantly defined a subgroup of size 73.24% (within the Vedolizumab arm) that showed statistical evidence (bootstrap adjusted p-value = 0.0010) of enhanced treatment effect on week 6 clinical remission.

Table 8. The 4-SNP Model.

SNP ID	Chromosome	Position	MAF	β	$2f(1-f)\beta^2$
rs1561573	1	48227943	0.4833	0.32	0.0512
rs6671927	1	48285768	0.3023	-0.4502	0.0855
rs2088361	1	48362713	0.4136	-0.6524	0.2065
rs1556981	1	48370525	0.1736	-0.8948	0.2298

The 4-variant (4-SNP) model shows statistically significant evidence for a treatment-specific effect. A subgroup identified via the genetic signature in Table 8 showed a statistically significant clinical remission treatment effect. See Figure 7A, where the left markings for vedolizumab and placebo represent patients “not in the subgroup,” the middle markings in each category represent the “treatment main effect,” and the right markings in each category represent patients “in the subgroup.” Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 7A. The subgroup showing enhanced treatment effect was identified using the parametric bootstrapping methods set forth in Example 2. In particular, responders were identified using the following formula, where the optimal cutoff was $\tau_* = -1.4350$:

$$Score_i = (\text{rs1561573 coefficient}) * \text{rs1561573} + (\text{rs6671927 coefficient}) * \text{rs6671927} + (\text{rs2088361 coefficient}) * \text{rs2088361} + (\text{rs1556981 coefficient}) * \text{rs1556981}$$

The specific algorithm used was as follows:

$$Score_i = 0.32 * \text{rs1561573} - 0.4502 * \text{rs6671927} - 0.6524 * \text{rs2088361} - 0.8948 * \text{rs1556981},$$

where the value for rs1561573, rs6671927, rs2088361, rs1556981, respectively, is 0, 1, or 2, depending on the number of the patient’s minor allele.

The distribution of Biomarker+ subgroup (In the subgroup) and Biomarker– subgroup (not in the subgroup) in vedolizumab- and placebo-treated CD patients is shown in Table 9.

Table 9: Distribution of Biomarker+ subgroup (in the subgroup) and Biomarker– subgroup (Not in the subgroup) CD patients

	Not in Subgroup (%)	In Subgroup (%)	Total
Placebo	73 (26.64)	201 (73.36)	274
Vedolizumab	91 (26.76)	249 (73.24)	340
Total	164 (26.71)	450 (73.29)	614

Figures 7B and 7C show clinical remission over time during the induction phase in the C13007 and C13011 trials, respectively.

Figure 7D shows a statistically significant enhanced clinical response treatment effect. See Figure 7D, where the left markings for vedolizumab and placebo represent patients “not in the subgroup,” the middle markings in each category represent the “treatment main effect,” and the right markings in each category represent patients “in the subgroup.” Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 7D. Figure 7E and 7F show enhanced clinical response over time in the C13007 and C13011 trials, respectively.

Figure 7G shows plots of CDAI scores versus genetic composite biomarker scores for both vedolizumab treatment and placebo treatment in the 4-SNP model. Figure 7H shows observed vs. predicted CDAI scores for the 4-SNP model.

Initial follow-up analysis on the 4-SNP model (conducted on a second cohort of the C13007 study that was not included in the initial analysis) was not consistent with the 4-SNP model being predictive of enhanced clinical response or clinical remission following treatment with vedolizumab. However, the follow-up analysis did trend toward showing a predictive effect at week 6 on clinical remission ($p = 0.071$), though it is possible this trend was driven by a negative effect of the placebo in the Biomarker+ group..

Example 6 – 5 SNP Models

Table 10 shows genes and gene combinations whose expression levels can be combined in multigene models that significantly correlate with clinical remission in adult Crohn's Disease patients treated with vedolizumab.

Table 10: 5 variants used in genetic signature.

SNP ID	MAF f	β	$2f(1-f)\beta^2$
rs1561573	0.4833	0.2738	0.0374
rs6671927	0.3023	-0.3913	0.0646
rs2088361	0.4136	-0.5404	0.1417
rs1556981	0.1736	-0.7396	0.157
rs11205430	0.3729	-0.1912	0.0171

The 5-variant (5-SNP) model shows statistically significant evidence for a treatment-specific effect. A subgroup identified via the genetic signature in Table 10 showed a statistically significant clinical remission treatment effect. See Figure 8A, where the left markings for vedolizumab and placebo represent patients “not in the subgroup” and the right markings in each category represent patients “in the subgroup.” Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 8A. The subgroup showing enhanced treatment effect was identified using the parametric bootstrapping methods set forth in Example 2. In particular, responders were identified using the following formula, where the optimal cutoff was $\tau_* = -1.3896$:

$$Score_i = (\text{rs1561573 coefficient}) * \text{rs1561573} + (\text{rs6671927 coefficient}) * \text{rs6671927} + (\text{rs2088361 coefficient}) * \text{rs2088361} + (\text{rs1556981 coefficient}) * \text{rs1556981} + (\text{rs11205430 coefficient}) * \text{rs11205430}$$

The specific algorithm used was as follows:

$$Score_i = 0.2738 * rs1561573 - 0.3913 * rs6671927 - 0.5404 * rs2088361 - 0.7396 * rs1556981 - 0.1912 * rs11205430,$$

where the value for rs1561573, rs6671927, rs2088361, rs1556981, and rs11205430, respectively, is 0, 1, or 2, depending on the number of the patient's minor allele.

The distribution of Biomarker+ subgroup (in the subgroup) and Biomarker- subgroup (not in the subgroup) in vedolizumab- and placebo-treated CD patients is shown in Table 11.

Table 11: Distribution of Biomarker+ subgroup (in the subgroup) and Biomarker- subgroup (Not in the subgroup) CD patients in a first 5-SNP model

Treatment	In the Subgroup	Not in the Subgroup
Vedolizumab	252 (74.12%)	88 (25.88%)
Placebo	200 (72.99%)	74 (27.01%)
Total	452 (73.62%)	162 (26.38%)

A second 5-variant (5-SNP) model also shows statistically significant evidence for a treatment-specific effect. A subgroup identified via the genetic signature in Table 12 showed a statistically significant clinical remission treatment effect. See Figure 8B, where the left markings for vedolizumab and placebo represent patients "not in the subgroup" and the right markings in each category represent patients "in the subgroup." Moreover, subjects outside the subgroup showed a statistically significant non-response effect. See Figure 8B.

Table 12: 5 variants used in genetic signature.

SNP ID	MAF	β	$2f(1-f) \beta^2$
rs1561573	0.4833	0.2865	0.0410
rs11211613	0.3070	-0.3678	0.0576
rs12061891	0.1454	-1.0079	0.2525
rs11211632	0.4410	-0.5831	0.1676
rs11205430	0.3729	-0.2351	0.0258

The subgroup showing enhanced treatment effect was identified using the parametric bootstrapping methods set forth in Example 2. In particular, responders were identified using the following formula, where the optimal cutoff was $\tau_* = -1.59103$:

$$Score_i = (\text{rs1561573 coefficient}) * \text{rs1561573} + (\text{rs11211613 coefficient}) * \text{rs11211613} + (\text{rs12061891 coefficient}) * \text{rs12061891} + (\text{rs11211632 coefficient}) * \text{rs11211632} + (\text{rs11205430 coefficient}) * \text{rs11205430}$$

The specific algorithm used was as follows:

$$Score_i = 0.2865 * \text{rs1561573} - 0.3678 * \text{rs11211613} - 1.0079 * \text{rs12061891} - 0.5831 * \text{rs11211632} - 0.2351 * \text{rs11205430},$$

where the value for rs1561573, rs11211613, rs12061891, rs11211632, and rs11205430, respectively, is 0, 1, or 2, depending on the number of the patient's minor allele.

The distribution of Biomarker+ subgroup (in the subgroup) and Biomarker- subgroup (not in the subgroup) in vedolizumab- and placebo-treated CD patients is shown in Table 13.

Table 13: Distribution of Biomarker+ subgroup (in the subgroup) and Biomarker- subgroup (Not in the subgroup) CD patients in a second 5-SNP model

Treatment	In the Subgroup	Not in the Subgroup
Vedolizumab	252(74.12%)	88(25.88%)
Placebo	202(73.72%)	72(26.28%)
Total	454(73.94%)	160(26.06%)

Example 7 – 11 SNP Model Validation Study

A validation analysis was conducted with the 11-SNP model set forth in Example 3. The analysis was conducted using data from a 2nd cohort of the C13007 study (*i.e.*, data not used in Example 3). The data from the 2nd cohort was compared against placebo data discussed in Example 3, because the 2nd cohort of the C13007 did not contain placebo data. A logistical regression model was used to test for the difference in treatment effect in Biomarker+ and Biomarker- subgroups.

Patients used in the validation analysis had some differences in their demographic and clinical characteristics from the patients in Example 3: the validation analysis (i) had more White and fewer Asian patients, and more patients from North America, (ii) had more patients that failed anti-TNF treatment prior to treatment with vedolizumab, and (iii) had a higher response rate for clinical remissions and enhanced clinical response at week 6. Demographic and clinical characteristic are compared in Figures 9A-C. Sample sizes in the respective studies were as shown in Table 14:

Table 14: Sample Sizes for C13007 Induction Phase Subpopulations

	Cohort 1 (Example 3)		Cohort 2
	Placebo	Vedolizumab	Vedolizumab
Intent-to-treat population	148	220	747
Clinical data BSSI received	123	176	572
Population that passed genotypic QC	121	174	563

Validation analysis of the 11-SNP model showed a nominally significant predictive effect at week 6 on clinical remission. See Figure 10, where the left markings for vedolizumab and placebo represent patients “not in the subgroup,” and the right markings in each category represent patients “in the subgroup,” and the center markings in each category represent the total number of analyzed patients. There is nevertheless a possibility that the interaction effect may be driven by the placebo arm. The observed predictive effect is summarized in Table 15.

Table 15: Summary of subgroup predictive effect at week 6 comparing cohort 2 and the placebo arm of cohort 1

Endpoint	Beta Estimate	Std. Error	P-value
Clinical Remission	2.3553	1.4970	0.0357
Enhanced Clinical Response	0.9173	0.5889	0.1043
Clinical Response	0.4339	0.4916	0.3754

The distribution of Biomarker+ (in the subgroup) and Biomarker- (not in the subgroup) in the vedolizumab and placebo-treated CD patients is shown in Table 16.

Table 16: Distribution of Biomarker+ subgroup and Biomarker- subgroup CD patients in the 11-SNP validation analysis:

Treatment	In the Subgroup	Not in the Subgroup	Total
Vedolizumab	88 (72.73%)	33 (27.27 %)	121
Placebo	388 (69.04%)	174 (30.96%)	562
Total	476 (69.69%)	207 (30.31%)	683

When placebo data is excluded from the validation analysis, the 11-SNP model still trended towards a treatment effect in the Biomarker+ subgroup with respect to clinical remission and clinical response. In the placebo-excluded analysis on clinical remission, the mean response rate in the treatment arm in the Biomarker+ subgroup was 0.172 (0.122, 0.238), and the mean
 5 response rate in the treatment arm in the Biomarker- subgroup was 0.151 (0.117, 0.193) (p-value = 0.5276, pseudo $R^2 = 0.087$). Subjects in the Biomarker+ subgroup were 1.141 times more likely to respond to treatment than subjects in the Biomarker- subgroup (using a different statistical model that accounts for the placebo arm, the response rate for subjects in the Biomarker+ subgroup was 1.146 times higher than for subjects in the Biomarker- subgroup). A
 10 summary of the placebo-excluded analysis is shown in Table 17.

Table 17: Summary of subgroup main effect at week 6 in cohort 2 using 11-SNP model

Endpoint	Estimate	Std. Error	p-value
Clinical remission	0.1575	0.2482	0.5276
Enhanced clinical response	-0.0360	0.2010	0.8578
Clinical response	0.1235	0.1892	0.5140

WHAT IS CLAIMED IS:

1. A method for treating Crohn's Disease in an individual, comprising administering vedolizumab to an individual identified as (i) *TRABD2B* variant positive, (ii) *PDC* variant positive, (iii) *NPY* variant positive, (iv) *ONECUT1* variant positive, (v) *DLG4* variant positive,
5 (vi) *CLDN7* variant positive, (vii) *ELP5* variant positive, or (viii) any combination of these.
2. The method of claim 1, wherein the treating comprises remission of Crohn's Disease.
3. The method of claim 1, wherein the individual is heterozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the
10 *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.
4. The method of claim 1, wherein the individual is homozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.
5. The method of claim 1, wherein the *TRABD2B* variant is selected from the group
15 consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939, rs6684538, and combinations thereof.
6. The method of claim 1, wherein the *PDC* variant is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, and combinations thereof.
- 20 7. The method of claim 1, wherein the *NPY* variant is selected from the group consisting of rs16141, rs3779477, rs16129, and combinations thereof.
8. The method of claim 1, wherein the *ONECUT1* variant is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, and combinations thereof.

9. The method of claim 1, wherein the *DLG4* variant is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, and combinations thereof.

10. The method of claim 1, wherein the *CLDN7* variant and/or *ELP5* variant is
5 rs2106842, exm1286317, rs2074217, rs222843, and combinations thereof.

11. The method of claim 1, wherein the individual is identified as *TRABD2B* variant positive.

12. The method of claim 11, wherein the individual has rs1556981, rs2088361, rs1561573, and rs6671927 variants.

10 13. The method of claim 11, wherein the individual has rs1556981, rs2088361, rs1561573, rs6671927, and rs11205430 variants.

14. The method of claim 11, wherein the individual has rs1561573, rs11211613, rs12061891, rs11211632, and rs11205430.

15 15. The method of claim 1, wherein the individual is identified as *TRABD2B* variant positive, *PDC* variant positive, *NPY* variant positive, *ONECUT1* variant positive, *CLDN7* variant positive, and *ELP5* variant positive.

16. The method of claim 14, wherein the individual has rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842 variants.

20 17. The method of claim 1, wherein the individual is identified as *TRABD2B* variant positive, *PDC* variant positive, *NPY* variant positive, *ONECUT1* variant positive, *DLG4* variant positive, *CLDN7* variant positive, and *ELP5* variant positive.

18. The method of claim 17, wherein the individual has rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842 variants.

19. A method for determining the likelihood that an individual suffering from Crohn's Disease will experience an enhanced treatment effect when treated with vedolizumab comprising: (i) assaying a biological sample obtained from an individual for the presence or absence of a *TRABD2B* variant and/or a *PDC* variant and/or a *NPY* variant and/or a *ONECUT1* variant and/or a *DLG4* variant and/or a *CLDN7* variant and/or a *ELP5* variant and (ii) detecting the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant, wherein the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant indicates an increased likelihood that the individual will experience an enhanced treatment effect.

20. The method of claim 19, wherein the individual is heterozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.

21. The method of claim 19, wherein the individual is homozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.

22. The method of claim 19, wherein the *TRABD2B* variant is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939, rs6684538, and combinations thereof.

23. The method of claim 19, wherein the *PDC* variant is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, and combinations thereof.

24. The method of claim 19, wherein the *NPY* variant is selected from the group consisting of rs16141, rs3779477, rs16129 and combinations thereof.

25. The method of claim 19, wherein the *ONECUT1* variant is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, and combinations thereof.

26. The method of claim 19, wherein the *DLG4* variant is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229 and combinations thereof.

27. The method of claim 19, wherein the *CLDN7* variant and/or *ELP5* variant is rs2106842, exm1286317, rs2074217, rs222843, and combinations thereof.

28. The method of claim 19, comprising detecting the presence of the *TRABD2B* variant.

29. The method of claim 28, comprising detecting the presence of rs1556981, rs2088361, rs1561573, and rs6671927 variants.

30. The method of claim 28, comprising detecting the presence of rs1556981, rs2088361, rs1561573, rs6671927, and rs11205430 variants.

31. The method of claim 28, comprising detecting the presence of rs1561573, rs11211613, rs12061891, rs11211632, and rs11205430.

32. The method of claim 19, comprising detecting the presence of the *TRABD2B* variant, the *PDC* variant, the *NPY* variant, the *ONECUT1* variant, *CLDN7* variant, and the *ELP5* variant.

33. The method of claim 31, comprising detecting the presence of rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842 variants.

34. The method of claim 19, comprising detecting the presence of the *TRABD2B* variant, the *PDC* variant, the *NPY* variant the *ONECUT1* variant, the *DLG4* variant, the *CLDN7* variant, and the *ELP5* variant.

35. The method of claim 34, comprising detecting the presence of rs7543124,
5 rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842 variants.

36. A method for determining the likelihood that an individual suffering from Crohn's Disease will respond favorably to treatment with vedolizumab comprising: (i) assaying a biological sample obtained from an individual for the presence or absence of a *TRABD2B* variant and/or a *PDC* variant and/or a *NPY* variant and/or a *ONECUT1* variant and/or a *DLG4* variant
10 and/or a *CLDN7* variant and/or a *ELP5* variant and (ii) detecting the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant, wherein the presence of the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant
15 and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant indicates an increased likelihood that the individual will respond favorably to vedolizumab.

37. The method of claim 36, wherein the individual is heterozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.

20 38. The method of claim 36, wherein the individual is homozygous for the *TRABD2B* variant and/or the *PDC* variant and/or the *NPY* variant and/or the *ONECUT1* variant and/or the *DLG4* variant and/or the *CLDN7* variant and/or the *ELP5* variant.

39. The method of claim 36, wherein the *TRABD2B* variant is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981,
25 rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939, rs6684538, and combinations thereof.

40. The method of claim 36, wherein the *PDC* variant is selected from the group consisting of rs1882926, rs11801527, rs12407957, rs10798041, and combinations thereof.

41. The method of claim 36, wherein the *NPY* variant is selected from the group consisting of rs16141, rs3779477, rs16129, and combinations thereof.

5 42. The method of claim 36, wherein the *ONECUT1* variant is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, rs2456525, and combinations thereof.

43. The method of claim 36, wherein the *DLG4* variant is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, rs929229, and
10 combinations thereof.

44. The method of claim 36, wherein the *CLDN7* variant or *ELP5* variant is rs2106842, exm1286317, rs2074217, rs222843, and combinations thereof.

45. The method of claim 36, comprising detecting the presence of the *TRABD2B* variant.

15 46. The method of claim 45, comprising detecting the presence of rs1556981, rs2088361, rs1561573, and rs6671927 variants.

47. The method of claim 45, comprising detecting the presence of rs1556981, rs2088361, rs1561573, rs6671927, and rs11205430 variants.

48. The method of claim 45, comprising detecting the presence of rs1561573,
20 rs11211613, rs12061891, rs11211632, and rs11205430.

49. The method of claim 36, comprising detecting the presence of the *TRABD2B* variant, the *PDC* variant, the *NPY* variant, the *ONECUT1* variant, *CLDN7* variant, and the *ELP5* variant.

50. The method of claim 49, comprising detecting the presence of rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842 variants.

51. The method of claim 36, comprising detecting the presence of the *TRABD2B* variant, the *PDC* variant, the *NPY* variant, the *ONECUT1* variant, the *DLG4* variant, the
5 *CLDN7* variant, and the *ELP5* variant.

52. The method of claim 51, comprising detecting the presence of rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842 variants.

53. A kit comprising: (i) at least one pair of primers that specifically hybridizes to a
10 genetic variant independently selected from the group consisting of rs1556981, rs2088361, rs1561573, and rs6671927, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

54. The kit of claim 53, wherein the kit comprises: a pair of primers that specifically hybridizes to rs1556981; a pair of primers that specifically hybridizes to rs2088361; a pair of
15 primers that specifically hybridizes to rs1561573; and a pair of primers that specifically hybridizes to rs6671927.

55. The kit of claim 53, wherein the kit further comprises a pair of primers that specifically hybridizes to rs11205430.

56. A kit comprising: (i) at least one pair of primers that specifically hybridizes to a
20 genetic variant independently selected from the group consisting of rs1561573, rs11211613, rs12061891, rs11211632, and rs11205430, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

57. A kit comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs7543124, rs2088361,

rs1556981, rs1882926, rs11801527, rs3779477, rs1899750, and rs2106842, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

58. A kit comprising: (i) at least one pair of primers that specifically hybridizes to a genetic variant independently selected from the group consisting of rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673, and rs2106842, and (ii) a detectably labeled probe that hybridizes to the genetic variant.

59. $\alpha 4\beta 7$ integrin antagonist for use in the treatment of a subject with Crohn's Disease, wherein the subject has been selected for treatment with said antagonist by having determined the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a sample having been obtained from said subject, wherein said determined presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

60. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 59, wherein the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

61. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 59 to 60, wherein the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

62. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 59 to 61, wherein the presence or absence of the single nucleotide polymorphisms rs2088361 and rs1556981 has been determined.

63. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 62, wherein the absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

64. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 59 to 63,
5 wherein the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573 has been determined.

65. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 64, wherein the absence of the single nucleotide polymorphisms rs6671927, rs2088361 and rs1556981 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response
10 to said $\alpha 4\beta 7$ integrin antagonist.

66. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 65, wherein the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:
 $Score_i = (0.32 * rs1561573) - (0.4502 * rs6671927) - (0.6524 * rs2088361) - (0.8948 * rs1556981),$

15 wherein the value for rs1561573, rs6671927, rs2088361 and rs1556981, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one alleles, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.4350 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

20 67. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 59 to 63, wherein the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573 has been determined.

68. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 67, wherein the absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs11205430 and the
25 presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

69. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 68, wherein the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:

$$Score_i = (0.2738 * rs1561573) - (0.3913 * rs6671927) - (0.5404 * rs2088361) - (0.7396 * rs1556981) - (0.1912 * rs11205430),$$

5 wherein the value for rs1561573, rs6671927, rs2088361, rs1556981 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.3896 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

10 70. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 59 to 61, wherein the presence or absence of the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632 has been determined.

71. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 70, wherein the absence of the single nucleotide polymorphisms rs11211613, rs12061891, rs11211632 and rs11205430 and
15 the presence of the single nucleotide polymorphism rs1561573 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

72. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 71, wherein the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:
$$Score_i = (0.2865 * rs1561573) - (0.3678 * rs11211613) - (1.0079 * rs12061891) - (0.5831 * rs11211632) - (0.2351 * rs11205430),$$

20 wherein the value for rs1561573, rs11211613, rs12061891, rs11211632 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.5910 has been selected for
25 treatment with said $\alpha 4\beta 7$ integrin antagonist.

73. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 59 to 61, wherein additionally the presence or absence of at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* has been determined.

5 74. $\alpha 4\beta 7$ integrin antagonist for the use according claim 73, wherein the presence or absence of at least one single nucleotide polymorphism in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* has been determined.

75. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 73 or 74, wherein the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting
10 of rs1882926, rs11801527, rs12407957, and rs10798041.

76. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 73 or 74, wherein the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129.

77. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 73 or 74, wherein the
15 single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, and rs2456525.

78. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 73 or 74, wherein the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229.

20 79. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 73 or 74, wherein the single nucleotide polymorphism in the *ELP5* genomic locus is selected from the group consisting of rs2106842, exm1286317, rs2074217, and rs222843.

80. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 73 to 79, wherein the presence or absence of the single nucleotide polymorphisms rs7543124, rs6671927,

rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842 has been determined.

81. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 80, wherein the absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

82. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 81, wherein the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:

$$Score_i = (-0.1797 * rs7543124) - (0.3707 * rs6671927) - (0.5741 * rs2088361) - (0.5848 * rs1556981) + (0.7127 * rs1882926) - (0.7024 * rs11801527) - (0.6841 * rs3779477) + (0.2158 * rs2440335) + (0.6147 * rs1899750) + (0.3475 * rs1875673) + (0.397 * rs2106842),$$

wherein the value for rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.2123 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

83. $\alpha 4\beta 7$ integrin antagonist for the use according to any one of claims 73 to 79, wherein the presence or absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 has been determined.

84. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 83, wherein the absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence of the single nucleotide polymorphisms rs1882926, rs1899750 and rs2106842 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist.

85. $\alpha 4\beta 7$ integrin antagonist for the use according to claim 84, wherein the subject has been selected for treatment with the $\alpha 4\beta 7$ integrin antagonist with the following formula:

$$Score_i = (-0.2213 * rs7543124) - (0.8735 * rs2088361) - (0.659 * rs1556981) + (0.8567 * rs1882926) - (0.858 * rs11801527) - (0.6935 * rs3779477) + (0.9288 * rs1899750) + (0.7159 * rs2106842)$$

wherein the value for rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.6803 has been selected for treatment with said $\alpha 4\beta 7$ integrin antagonist.

86. Method for predicting a treatment response to an $\alpha 4\beta 7$ integrin antagonist in a subject with Crohn's Disease, said method comprising the step of determining the presence or absence of at least one single nucleotide polymorphism in the *TRABD2B* genomic locus in a nucleic acid sample obtained from said subject, wherein the presence or absence of the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

87. Method according to claim 86, wherein the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

88. Method according to any one of claims 86 to 87, wherein the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

89. Method according to any one of claims 86 to 88, wherein the presence or absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is determined.

90. Method according to claim 89, wherein the absence of the single nucleotide polymorphisms rs2088361 and rs1556981 is predictive for the subject's treatment response to said $\alpha 4\beta 7$ integrin antagonist

91. Method according to any one of claims 86 to 90, wherein the presence or absence
5 of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573 is determined.

92. Method according to claim 91, wherein the absence of the single nucleotide polymorphisms rs6671927, rs2088361 and rs1556981 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin
10 antagonist.

93. Method according to claim 92, wherein a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (0.32 * rs1561573) - (0.4502 * rs6671927) - (0.6524 * rs2088361) - (0.8948 * rs1556981),$$

15 wherein the value for rs1561573, rs6671927, rs2088361 and rs1556981, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.4350 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

20 94. Method according to any one of claims 86 to 90, wherein the presence or absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573 is determined.

95. Method according to claim 94, wherein the absence of the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs11205430 and the presence of the single
25 nucleotide polymorphism rs1561573 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

96. Method according to claim 95, wherein a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (0.2738 * rs1561573) - (0.3913 * rs6671927) - (0.5404 * rs2088361) - (0.7396 * rs1556981) - (0.1912 * rs11205430),$$

5 wherein the value for rs1561573, rs6671927, rs2088361, rs1556981 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.3896 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

10 97. Method according to any one of claims 86 to 88, wherein the presence or absence of the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632 is determined.

15 98. Method according to claim 97, wherein the absence of the single nucleotide polymorphisms rs11211613, rs12061891, rs11211632 and rs11205430 and the presence of the single nucleotide polymorphism rs1561573 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

99. Method according to claim 98, wherein a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (0.2865 * rs1561573) - (0.3678 * rs11211613) - (1.0079 * rs12061891) - (0.5831 * rs11211632) - (0.2351 * rs11205430),$$

20 wherein the value for rs1561573, rs11211613, rs12061891, rs11211632 and rs11205430, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than -1.5910 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

25

100. Method according to any one of claims 86 to 88, wherein additionally the presence or absence of at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* is determined.

101. Method according claim 100, wherein the presence or absence of at least one
5 single nucleotide polymorphism in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5* is determined.

102. Method according to claim 100 or 101, wherein the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926, rs11801527, rs12407957, and rs10798041.

103. Method according to claim 100 or 101, wherein the single nucleotide
10 polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129.

104. Method according to claim 100 or 101, wherein the single nucleotide
polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of
15 rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, and rs2456525.

105. Method according to claim 100 or 101, wherein the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229.

106. Method according to claim 100 or 101, wherein the single nucleotide
20 polymorphism in the *ELP5* genomic locus is selected from the group consisting of rs2106842, exm1286317, rs2074217, and rs222843.

107. Method according to any one of claims 100 to 106, wherein the presence or absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981,

rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842 is determined.

108. Method according to claim 107, wherein the absence of the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs11801527 and rs3779477 and
5 the presence of the single nucleotide polymorphisms rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

109. Method according to claim 108, wherein a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (-0.1797 * rs7543124) - (0.3707 * rs6671927) - (0.5741 * rs2088361) - (0.5848 * rs1556981) + (0.7127 * rs1882926) - (0.7024 * rs11801527) - (0.6841 * rs3779477) + (0.2158 * rs2440335) + (0.6147 * rs1899750) + (0.3475 * rs1875673) + (0.397 * rs2106842),$$

wherein the value for rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842, respectively, is 2 if the single
15 nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.2123 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

110. Method according to any one of claims 100 to 106, wherein the presence or
20 absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 is determined.

111. Method according to claim 110, wherein the absence of the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs11801527 and rs3779477 and the presence
25 of the single nucleotide polymorphisms rs1882926, rs1899750 and rs2106842 is predictive for the treatment response to said $\alpha 4\beta 7$ integrin antagonist.

112. Method according to claim 111 wherein a subject that is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy is identified with the following formula:

$$Score_i = (-0.2213 * rs7543124) - (0.8735 * rs2088361) - (0.659 * rs1556981) + (0.8567 * rs1882926) - (0.858 * rs11801527) - (0.6935 * rs3779477) + (0.9288 * rs1899750) + (0.7159 * rs2106842)$$

wherein the value for rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842, respectively, is 2 if the single nucleotide polymorphism is present in both alleles, 1 if the single nucleotide polymorphism is present in one allele, and 0 if the single nucleotide polymorphism is not present and wherein a subject having a score of more than 0.6803 is likely to respond to $\alpha 4\beta 7$ integrin antagonist therapy.

113. A group of biomarkers comprising SNP rs2088361 and SNP rs1556981.

114. Group of biomarkers according to claim 113, further comprising at least two SNPs selected from the group consisting of rs7543124, rs6671927, rs1561573 and rs11205430.

115. Group of biomarkers according to claim 113 or 114, consisting of SNPs rs6671927, rs2088361, rs1556981 and rs1561573.

116. Group of biomarkers according to claim 113 or 114, consisting of SNPs rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573.

117. Group of biomarkers according to claim 113 or 114, further comprising SNPs rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842.

118. Group of biomarkers according to claim 117, consisting of SNPs rs7543124, rs6671927, rs2088361, rs1556981, rs11801527, rs3779477, rs1882926, rs2440335, rs1899750, rs1875673 and rs2106842.

119. Group of biomarkers according to claim 113, further comprising SNPs rs7543124, rs11801527, rs3779477, rs1882926, rs1899750, and rs2106842.

120. Group of biomarkers according to claim 119, consisting of SNPs rs2088361, rs1556981, rs7543124, rs11801527, rs3779477, rs1882926, rs1899750, and rs2106842.

121. A group of biomarkers, comprising SNPs rs11205430, rs1561573, rs11211613, rs12061891 and rs11211632.

5 122. Kit, diagnostic composition or device comprising a probe selective for at least one single nucleotide polymorphism in the *TRABD2B* genomic locus.

123. Kit, diagnostic composition or device according to claim 122, wherein the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981,
10 rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

124. Kit, diagnostic composition or device according to claim 122 or 123, comprising probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573.

125. Kit, diagnostic composition or device according to claim 122 or 123, comprising
15 probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573.

126. Kit, diagnostic composition or device according to claim 122 or 123, comprising probes selective for the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632.

20 127. Kit, diagnostic composition or device according to claim 122 or 123, further comprising a probe selective for at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

128. Kit, diagnostic composition or device according to claim 127, further comprising probes selective for at least one single nucleotide polymorphism in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

129. Kit, diagnostic composition or device according to claim 127 or 128, wherein the
5 single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926, rs11801527, rs12407957, and rs10798041.

130. Kit, diagnostic composition or device according to claim 127 or 128, wherein the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129.

10 131. Kit, diagnostic composition or device according to claim 127 or 128, wherein the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, and rs2456525.

132. Kit, diagnostic composition or device according to claim 127 or 128, wherein the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group
15 consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229.

133. Kit, diagnostic composition or device according to claim 127 or 128, wherein the single nucleotide polymorphism in the *ELP5* genomic locus is selected from the group consisting of rs2106842, exm1286317, rs2074217, and rs222843.

134. Kit, diagnostic composition or device according to any one of claims 127 to 133,
20 comprising probes selective for the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842.

135. Kit, diagnostic composition or device according to any one of claims 127 to 133, comprising probes selective for the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842.

5 136. Kit, diagnostic composition or device according to any one of claims 122 to 135, further comprising an enzyme for primer elongation, nucleotides and/or labeling agents.

137. Microarray comprising a probe selective for at least one single nucleotide polymorphism in the *TRABD2B* genomic locus.

10 138. Microarray according to claim 137, wherein the at least one single nucleotide polymorphism in the *TRABD2B* genomic locus is selected from the group consisting of rs7543124, rs6671927, rs12134443, rs11211624, rs2088361, rs1556981, rs11205430, rs1561573, rs11211613, rs12061891, rs11211632, rs17103939 and rs6684538.

139. Microarray according to claim 137 or 138, comprising probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981 and rs1561573.

15 140. Microarray according to claim 137 or 138, comprising probes selective for the single nucleotide polymorphisms rs6671927, rs2088361, rs1556981, rs11205430 and rs1561573.

141. Microarray according to claim 137 or 138, comprising probes selective for the single nucleotide polymorphisms rs11205430, rs1561573, rs11211613, rs12061891, rs11211632.

20 142. Microarray according to claim 137 or 138, further comprising a probe selective for at least one single nucleotide polymorphism in at least one genomic locus selected from the group consisting of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

143. Microarray according to claim 142, further comprising probes selective for the single nucleotide polymorphisms in each of the genomic loci of *PDC*, *NPY*, *ONECUT1*, *DLG4* and *ELP5*.

144. Microarray according to claim 142 or 143, wherein the single nucleotide polymorphism in the *PDC* genomic locus is selected from the group consisting of rs1882926, rs11801527, rs12407957, and rs10798041.

145. Microarray according to claim 142 or 143, wherein the single nucleotide polymorphism in the *NPY* genomic locus is selected from the group consisting of rs16141, rs3779477, and rs16129.

146. Microarray according to claim 142 or 143, wherein the single nucleotide polymorphism in the *ONECUT1* genomic locus is selected from the group consisting of, rs2440335, rs2440332, rs1899750, rs7180600, rs2456507, and rs2456525.

147. Microarray according to claim 142 or 143, wherein the single nucleotide polymorphism in the *DLG4* genomic locus is selected from the group consisting of rs17203281, rs3826408, rs1875673, rs739669, rs2017365, and rs929229.

148. Microarray according to claim 142 or 143, wherein the single nucleotide polymorphism in the *ELP5* genomic locus is selected from the group consisting of rs2106842, exm1286317, rs2074217, and rs222843.

149. Microarray according to any one of claims 142 to 148, comprising probes selective for the single nucleotide polymorphisms rs7543124, rs6671927, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs2440335, rs1899750, rs1875673 and rs2106842.

150. Microarray according to any one of claims 142 to 148, comprising probes selective for the single nucleotide polymorphisms rs7543124, rs2088361, rs1556981, rs1882926, rs11801527, rs3779477, rs1899750 and rs2106842 is determined.

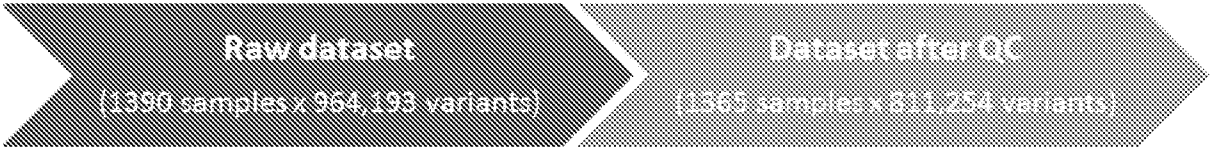
151. Use of the group of biomarkers according to any one of claims 113 to 121, the kit, diagnostic composition or device according to any one of claims 122 to 136 or of the microarray

according to any one of claims 137 to 150 for predicting a patient's response to treatment with a $\alpha 4\beta 7$ integrin antagonist.

152. Use of the group of biomarkers according to any one of claims 113 to 121, the kit, diagnostic composition or device according to any one of claims 122 to 136 or of the microarray
5 according to any one of claims 137 to 150 for identifying a patient with Crohn's Disease as being eligible for treatment with a $\alpha 4\beta 7$ integrin antagonist.

153. Use according to claim 151 or 152, wherein the $\alpha 4\beta 7$ integrin antagonist is vedolizumab.

Summary of Genotypic QC



Race	N (after QC)
AMERICAN INDIAN OR ALASKAN NATIVE	4
ASIAN (INDIA)	59
ASIAN (OTHER)	24
ASIAN (SOUTH KOREA)	56
BLACK	25
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2
Not Reported	1
Other	8
White	1186

FIGURE 1A

Baseline Character	List of Characteristics	PLA (N=275)	Treatment Arm(s) V02 (N=341)	Overall (N=616)
Study	C13007	121 (44.00 %)	174 (51.03 %)	295 (47.89 %)
	C13011	154 (56.00 %)	167 (48.97 %)	321 (52.11 %)
Previous Treatment	No Oral Corticosteroid, No Previous TNF or IMM	34 (12.36 %)	41 (12.02 %)	75 (12.18 %)
	No Oral Corticosteroid, Previous TNF or IMM	101 (36.73 %)	131 (38.42 %)	232 (37.66 %)
	Oral Corticosteroid, No Previous TNF or IMM	26 (9.45 %)	35 (10.26 %)	61 (9.90 %)
	Oral Corticosteroid, Previous TNF or IMM	114 (41.45 %)	134 (39.30 %)	248 (40.26 %)
Region	AFRICA ASIA AUSTRALIA	33 (12.00 %)	56 (16.42 %)	89 (14.45 %)
	CENTRAL EUROPE	72 (26.18 %)	76 (22.29 %)	148 (24.03 %)
	EASTERN EUROPE	12 (4.36 %)	22 (6.45 %)	34 (5.52 %)
	NORTH AMERICA	105 (38.18 %)	131 (38.42 %)	236 (38.31 %)
	WESTERN/NORTHERN EUROPE	53 (19.27 %)	56 (16.42 %)	109 (17.69 %)
	F	155 (56.36 %)	184 (53.96 %)	339 (55.03 %)
Sex	M	120 (43.64 %)	157 (46.04 %)	277 (44.97 %)
	N	274	340	614
Baseline CDAI	Mean (SD)	308.87 (83.87)	320.62 (62.23)	315.38 (63.19)
	Min	155	132	132
	Median	301	314.5	310
	Max	584	524	584
	N	275	341	616
Age	Mean (SD)	37.93 (12.89)	37.51 (11.95)	37.7 (12.37)
	Min	18.6	18.4	18.4
	Median	36.1	36.2	36.1
	Max	77.1	77.3	77.3

FIGURE 1B

Gene-level Scan Top Results in All Patients for Clinical Remission (N=614)

Gene ID	Tier	chr	start - end	P(interaction)/ adjusted ^a	P(main effect in two arms)	P(main effect in treated)	P(main effect in placebo)
TRABD2B	1	1	48221129-48467562	0.0002 / 0.1909	0.0632	0.0005	0.0716
CLDN7	2	17	7158221-7171512	0.0012 / 1.000	0.0746	0.0023	0.1266
GABARAP	2	17	7138737-7150753	0.0012 / 1.000	0.0881	0.0029	0.1321
ELP5	1	17	7150371-7168259	0.0016 / 1.000	0.0526	0.0021	0.1255
CTDNEP1	2	17	7141905-7160259	0.0021 / 1.000	0.0536	0.0031	0.1395
POC	2	1	186407697-186435240	0.0023 / 1.000	0.0399	0.002	0.463
DLG4	2	17	7088209-7128369	0.0026 / 1.000	0.027	0.0018	0.1961
MIR324	2	17	7121615-7131698	0.003 / 1.000	0.0833	0.0027	0.2139
ONECUT1	2	15	53044159-53067209	0.0033 / 1.000	0.0296	0.0028	0.2262
NPY	2	7	24318806-24336484	0.004 / 1.000	0.0084	0.0005	0.4817

FIGURE 2A

Gene-level Top Results in C13007 for Clinical Remission (N=293)

Gene ID	Tier	Chr	Start - end	P(interaction)	P(main effect in treated arm)	P(main effect in treated)	P(main effect in placebo)
TRABD2B	1	1	48221199-48467562	0.049	0.7737	0.1412	0.7703
CLDN7	2	17	7158221-7171512	0.0323	0.0679	0.0137	0.1422
GABARAP	2	17	7138737-7150753	0.0327	0.1256	0.0268	0.1422
ELP5	1	17	7150371-7168259	0.031	0.076	0.0145	0.1436
CTDNEP1	2	17	7141905-7160259	0.0449	0.1355	0.0334	0.1908
PDC	2	1	186407697-186435240	0.4477	0.3616	0.2605	0.9657
DLG4	2	17	7088209-7128369	0.0296	0.1093	0.0222	0.3354
MIR324	2	17	7121615-7131698	0.028	0.1196	0.0197	0.2105
CNECUT1	2	15	53044159-53087209	0.0007	0.667	0.0705	0.0306
NPY	2	7	24318806-24336484	0.0152	0.0147	0.008	0.295

FIGURE 2B

Gene-level Top Results in C13011 for Clinical Remission (N=321)

Gene ID	Tier	chr	start-end	P (association)	P (association in two arms)	P (association in treated)	P (association in placebo)
TRABD2B	1	1	48221199-48467562	0.0044	0.1461	0.0055	0.1434
CLDN7	2	17	7158221-7171512	0.0171	0.2534	0.0328	0.4165
GABARAP	2	17	7138737-7150753	0.0173	0.2429	0.0316	0.4263
ELPS	1	17	7150371-7168259	0.0213	0.1866	0.0358	0.4341
CTDNBP1	2	17	7141905-7160259	0.0253	0.1602	0.0395	0.4284
PDC	2	1	186407697-186435240	0.0005	0.0608	0.0009	0.3156
DLG4	2	17	7088209-7128369	0.0594	0.1961	0.065	0.3958
MIR324	2	17	7121615-7131698	0.0512	0.3672	0.0556	0.5412
ONECUT1	2	15	53044159-53087209	0.3279	0.0542	0.0505	0.3586
NPY	2	7	24318806-24336484	0.0697	0.2951	0.0525	0.8764

FIGURE 2C

Gene-level Top Results in Caucasians for Clinical Remission (N=537)

Gene ID	Tier	Chr	Gene coord	P(interaction)	P(main effect in treated arm)	P(main effect in treated)	P(main effect in placebo)
IRAB02B	1	1	48221199-48467562	0.0006	0.0559	0.0012	0.065
CLDN7	2	17	7158221-7171512	0.0022	0.0377	0.0005	0.1971
GABARAP	2	17	7138737-7150753	0.0022	0.0365	0.0005	0.204
ELP5	1	17	7150371-7168259	0.0032	0.0219	0.0005	0.1822
CTDNEP1	2	17	7141905-7160259	0.004	0.0219	0.0007	0.1685
PDC	2	1	186407697-186435240	0.0015	0.0158	0.001	0.4946
DLG4	2	17	7088209-7128369	0.001	0.0128	0.0002	0.2576
MIR324	2	17	7121615-7131698	0.0008	0.032	0.0002	0.2115
ONECUT1	2	15	53044158-53087209	0.0128	0.1132	0.0149	0.1935
NPY	2	7	24318806-24336484	0.0029	0.0087	0.0007	0.4113

FIGURE 2D

Gene-level Scan Top Results in All Patients for Enhanced Clinical Response (N=614)

Gene ID	Tier	chr	chr_start-end	P(heterozygosity) adjusted ^a	Z(homo effect in two arms)	Z(homo effect in treated)	Z(homo effect in placebo)
CSort20	1	5	134774903-134788038	0.0011 / 1.000	0.0397	0.0032	0.0207
CLNS	1	13	77561058-77581652	0.0017 / 1.000	0.0715	0.0002	0.596
COL24A1	1	1	86189915-86627121	0.0018 / 1.000	0.0898	0.0021	0.0728
TIFAB	2	5	134779557-134793089	0.0018 / 1.000	0.0548	0.0067	0.019
PLAGL1	2	6	144256436-144390735	0.0025 / 1.000	0.0624	0.0027	0.145
CEP72	1	5	607404-658666	0.0027 / 1.000	0.015	0.0798	0.0002
FBXL3	1	13	77574388-77606331	0.003 / 1.000	0.0346	0.0001	0.8668
PAPOLG	1	2	60978364-61034221	0.0038 / 1.000	0.0566	0.0026	0.6979
SLC47A1	2	17	19432166-19487346	0.0043 / 1.000	0.0376	0.0006	0.9473
WRAP53	2	17	7584388-7611820	0.0046 / 1.000	0.0042	0.0002	0.9658

FIGURE 3A

Gene-level Top Results in C13007 for Enhanced Clinical Response (N=293)

Gene ID	Tier	Q1*	start - end	P(interaction)	P(main effect in test arm)	P(main effect in treated)	P(main effect in placebo)
C5orf20	1	1	48221199-48467562	0.1735	0.5985	0.4073	0.305
CLN5	2	17	7158221-7171512	0.0063	0.6378	0.0118	0.2199
COL24A1	2	17	7138737-7150753	0.0286	0.0594	0.003	0.7373
TIFAB	1	17	7150371-7168259	0.0812	0.4432	0.2736	0.132
PLAGL1	2	17	7141905-7160259	0.0329	0.6295	0.1433	0.3878
CEP72	2	1	186407697-186435240	0.3766	0.0248	0.0831	0.0682
FBXL3	2	17	7088209-7128369	0.0048	0.8558	0.0066	0.2863
PAPOLG	2	17	7121615-7131698	0.0004	0.1029	0.0016	0.1813
SLC47A1	2	15	53044159-53087209	0.0791	0.3209	0.0647	0.7642
WRAP53	2	7	24318806-24336484	0.0955	0.0758	0.0276	0.9223

FIGURE 3B

Gene-level Top Results in C13011 for Enhanced Clinical Response (N=321)

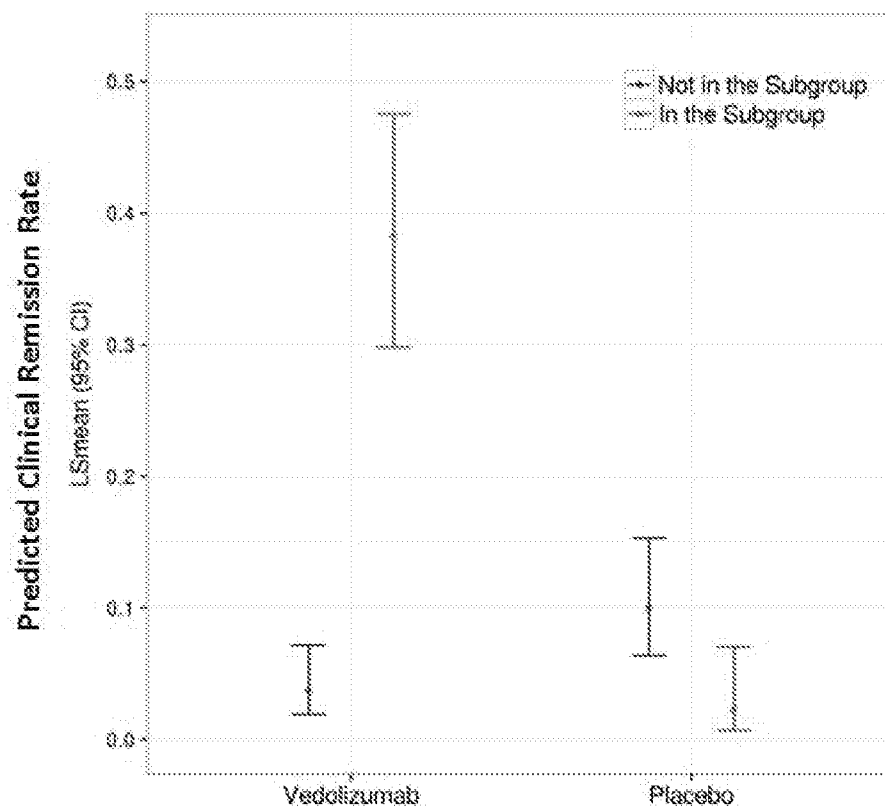
Gene ID	Tier	chr	start - end	[Homozygosity]	[Primary effect in two arms]	[Primary effect in treated]	[Primary effect in placebo]
C5orf20	1	1	48221199-48467562	0.0008	0.2258	0.0037	0.0365
CLNS	2	17	7158221-7171512	0.1019	0.0376	0.0253	0.141
COL24A1	2	17	7138737-7150753	0.0939	0.3335	0.1056	0.0733
TIFAB	1	17	7150371-7168259	0.0029	0.2652	0.0064	0.098
PLAGL1	2	17	7141905-7160259	0.021	0.0599	0.0045	0.1955
CEP72	2	1	186407697-186435240	0.0019	0.134	0.0216	0.0025
FBXL3	2	17	7088209-7128389	0.1819	0.0264	0.0277	0.2612
PAPOLG	2	17	7121615-7131698	0.1134	0.7067	0.2007	0.3157
SLC47A1	2	15	53044159-53087209	0.0453	0.0128	0.0045	0.8711
WRAP53	2	7	24318806-24336484	0.0258	0.0332	0.0041	0.8905

FIGURE 3C

Gene-level Top Results in Caucasians for Enhanced Clinical Response (N=537)

GeneID	Tier	chr	start-end	P(interaction)	P(main effect in top arm)	P(main effect in treated)	P(main effect in placebo)
C5orf29	1	1	48221199-48167562	0.0042	0.0398	0.0262	0.0067
CLN5	2	17	7158221-7171512	0.0019	0.141	0.0009	0.6396
COL24A1	2	17	7138737-7150753	0.0011	0.2438	0.0175	0.0625
TIFAB	1	17	7150371-7168259	0.0041	0.0342	0.0289	0.0055
PLAGL1	2	17	7141905-7160259	0.001	0.0785	0.002	0.07
CEP72	2	1	186407697-186435240	0.0358	0.0297	0.1317	0.002
FBXL3	2	17	7088209-7128369	0.0035	0.0796	0.0006	0.8321
PAPOLG	2	17	7121615-7131698	0.0043	0.0596	0.0042	0.2877
SLC47A1	2	15	53044159-53087209	0.0038	0.0198	0.0006	0.9374
WRAP53	2	7	24318806-24336484	0.0362	0.0011	0.0002	0.8599

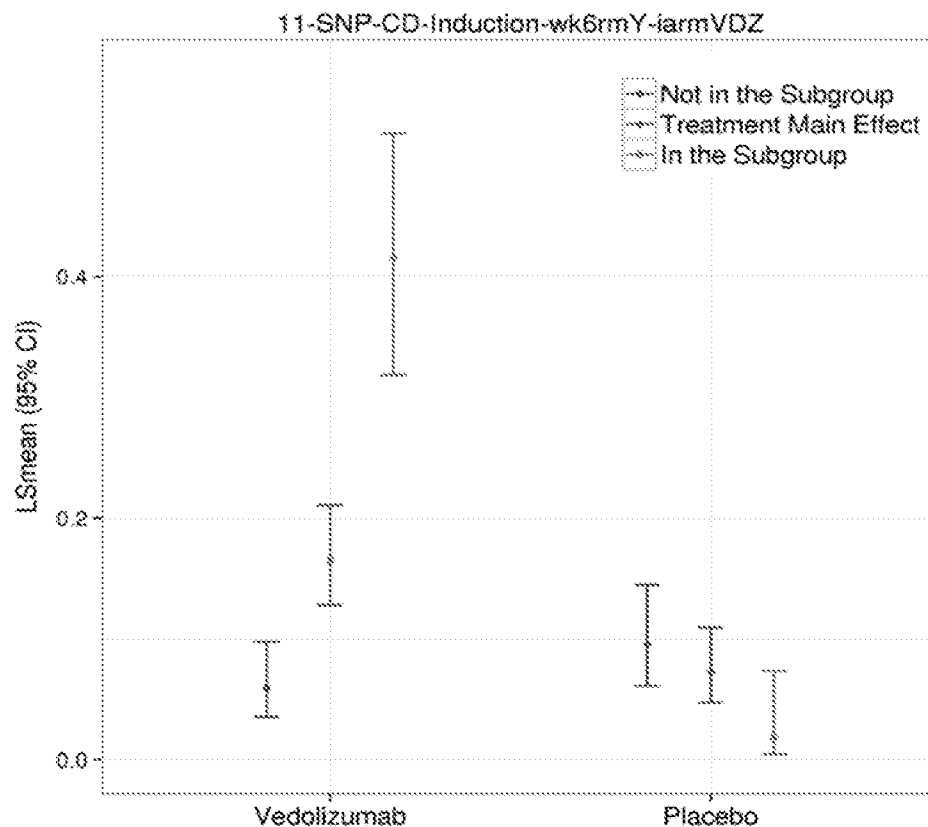
FIGURE 3D

Initial 19-SNP Model Identified for Clinical Remission

- Subgroup size: 38.82% (within Vedo arm)
- Tx OR w/in subgroup: 26.83 (7.76,92.77)
Tx OR outside subgroup: 0.35 (0.15,0.8)
Tx by subgroup interaction p-value: 0.0010
Mean response rate in Tx arm within subgroup: 0.38 (0.30, 0.48)
Mean response rate in Tx arm outside subgroup: 0.04 (0.02, 0.07)
=> 10.3 times more likely to respond

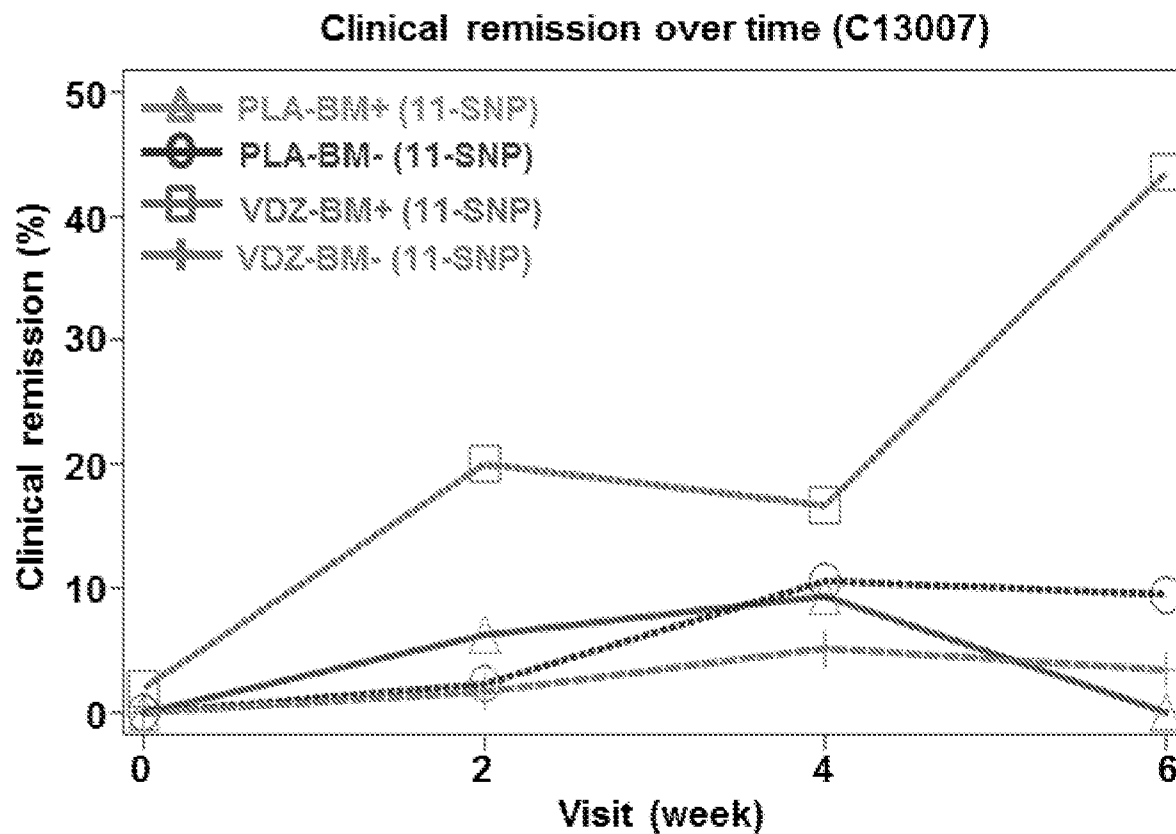
FIGURE 4

11-SNP Model: Clinical Remission of Crohn's Disease



- Clinical remission: CDAI score ≤ 150 points
 - Subgroup size: 30.88% (within Vedo arm)
 - Tx OR w/in subgroup (BM+): 37.38 (8.44,165.48)
 - Tx OR outside subgroup (BM-): 0.60 (0.30,1.20)
 - Tx by subgroup interaction p-value: **<0.0002^a**
 - Tx RD w/in subgroup: 0.4023 (0.3010,0.5035)
 - Tx RD outside subgroup: -0.0531 (-0.1088,0.0026)
 - Tx by subgroup Breslow p-value: **1.8e-09^b**
 - Mean response rate in Tx arm BM+: 0.4147 (0.3182, 0.5183)
 - Mean response rate in Tx arm BM-: 0.0594 (0.0355, 0.0976)
 - **~7.0 times more likely to respond when BM⁺**
 - Pseudo R²: 0.217
- ^aBootstrap-adjusted P-value
^bUnadjusted P-value

FIGURE 5A



Note:

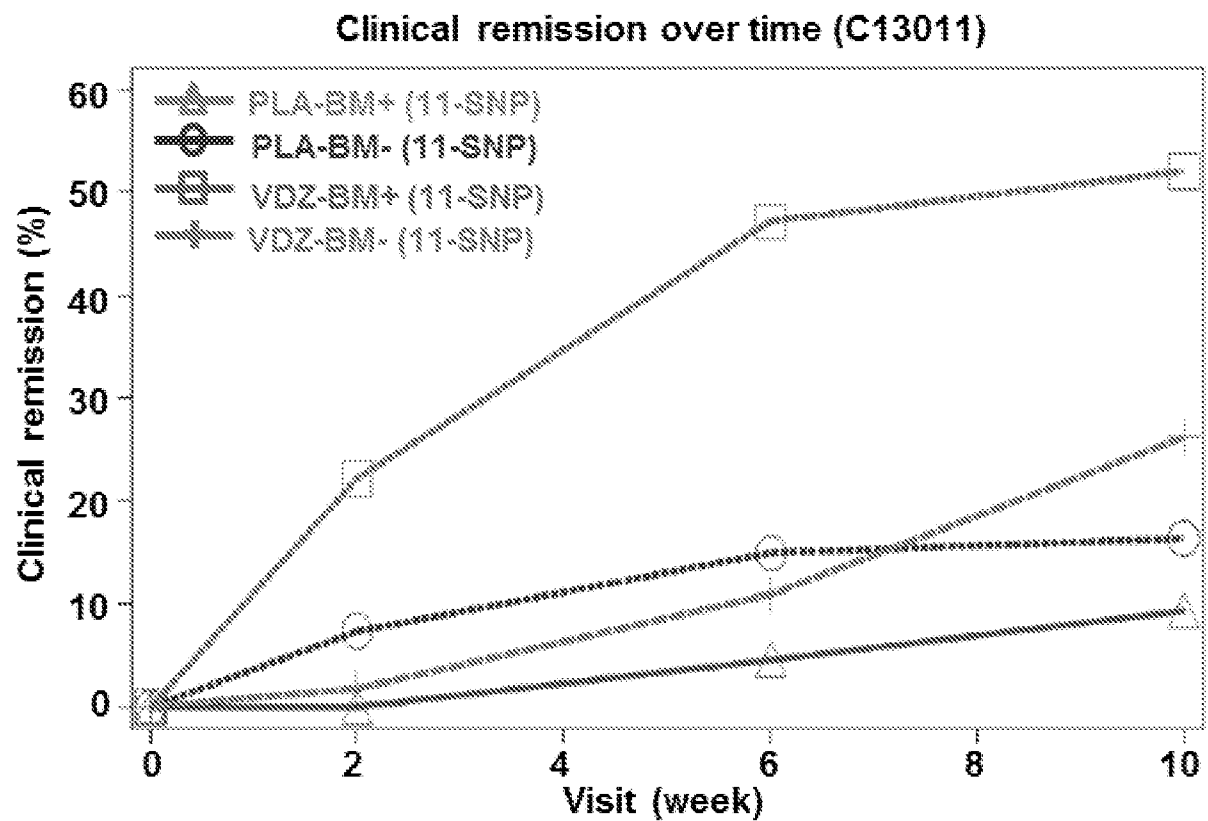
PLA BM+ at Week0 N=32, at Week6 N=32

PLA BM- at Week0 N=88, at Week6 N=84

VDZ BM+ at Week0 N=51, at Week6 N=46

VDZ BM- at Week0 N=122, at Week6 N=117

FIGURE 5B



Note:

PLA BM+ at Week0 N=44, at Week10 N=43

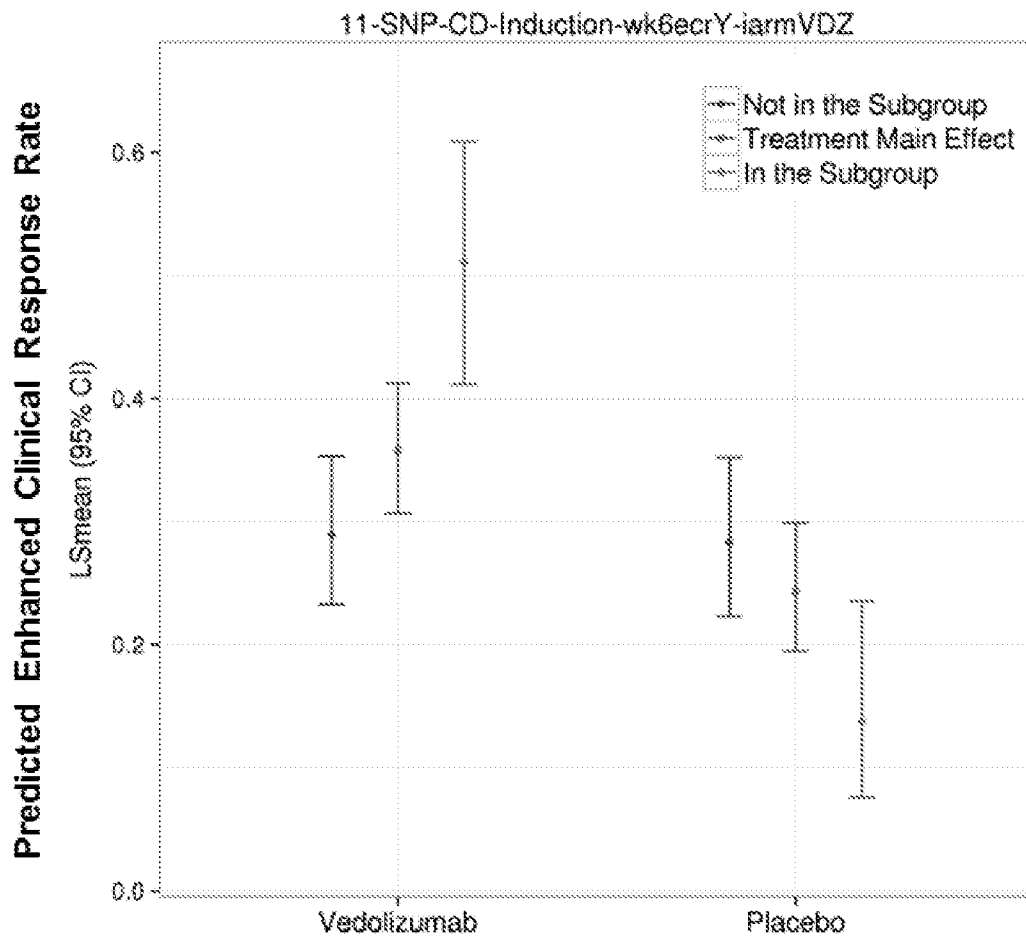
PLA BM- at Week0 N=110, at Week10 N=104

VDZ BM+ at Week0 N=54, at Week10 N=50

VDZ BM- at Week0 N=113, at Week10 N=107

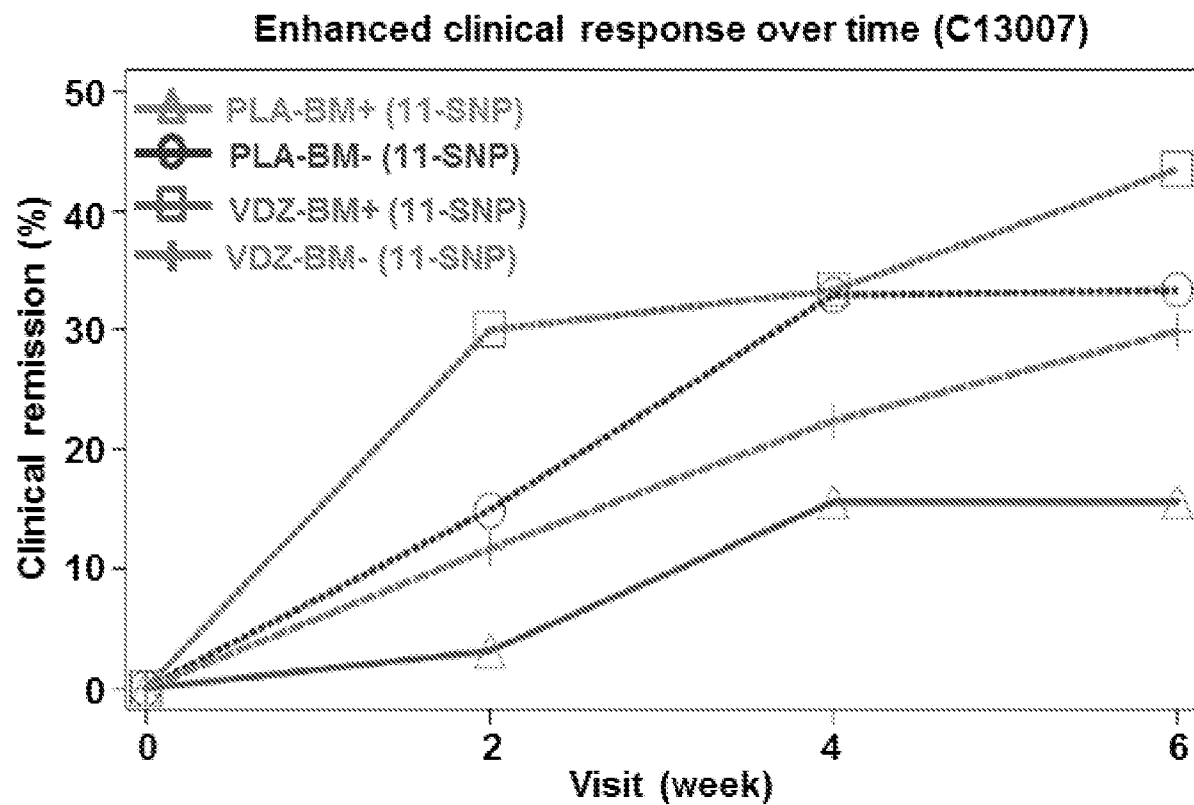
FIGURE 5C

11-SNP Model: Enhanced Clinical Response



- Enhanced clinical response: A ≥ 100 -point decrease in CDAI score from baseline (Week 0)
- Subgroup size in Tx Arm: 30.88%
- Tx OR in BM+: 6.53 (3.03, 14.08)
- Tx OR in BM-: 1.03 (0.67, 1.59)
- Tx by subgroup interaction p-value: **1.5e-05**
- Tx RD in BM+: 0.36 (0.24, 0.48)
- Tx RD in BM-: 0.01 (-0.08, 0.10)
- Tx by subgroup Breslow p-value: **3.3e-05**
- Mean response rate in BM+: 0.5106 (0.4118, 0.6085)
- Mean response rate in BM-: 0.2893 (0.2328, 0.3533)
- ~1.76 times more likely to respond
- Pseudo R^2 : 0.087

FIGURE 5D



Note:

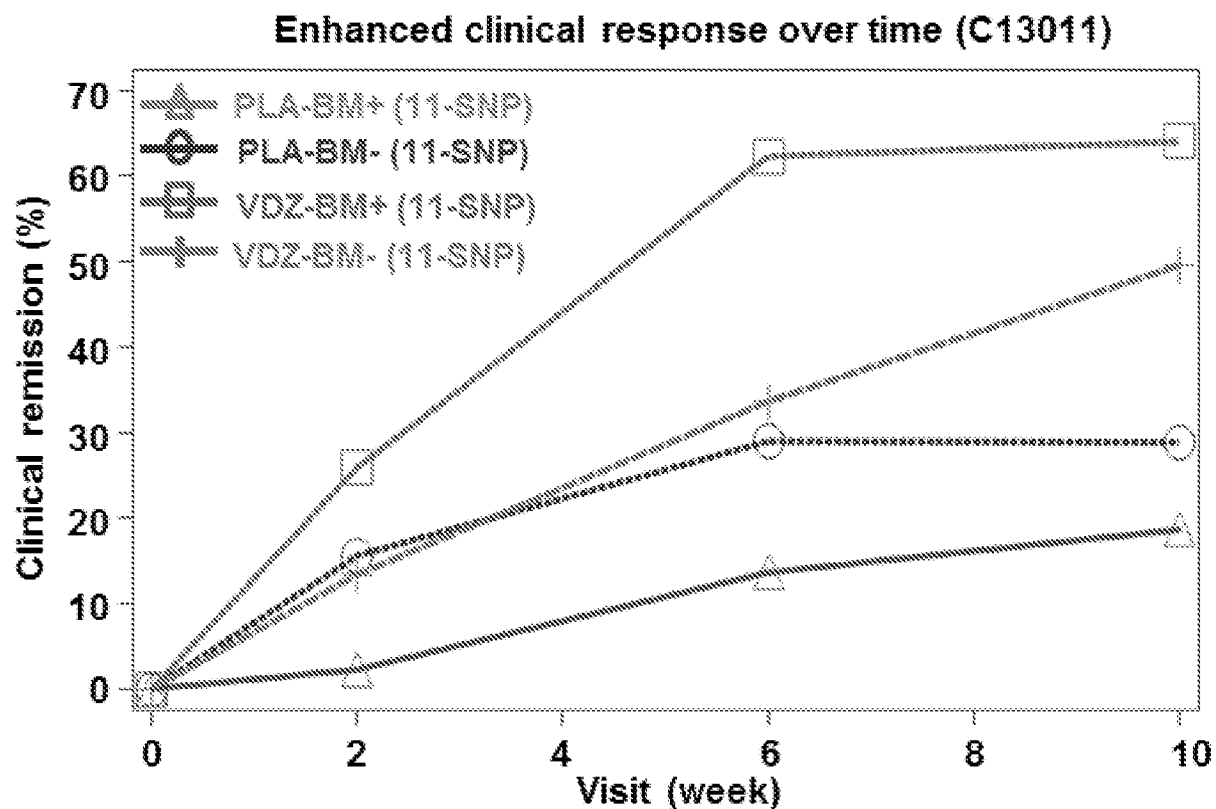
PLA BM+ at Week0 N=32, at Week6 N=32

PLA BM- at Week0 N=88, at Week6 N=84

VDZ BM+ at Week0 N=51, at Week6 N=46

VDZ BM- at Week0 N=122, at Week6 N=117

FIGURE 5E



Note:

PLA BM+ at Week0 N=44, at Week10 N=43

PLA BM- at Week0 N=110, at Week10 N=104

VDZ BM+ at Week0 N=54, at Week10 N=50

VDZ BM- at Week0 N=113, at Week10 N=107

FIGURE 5F

11-SNP Model: CDAI Score vs. Genetic Biomarker Score

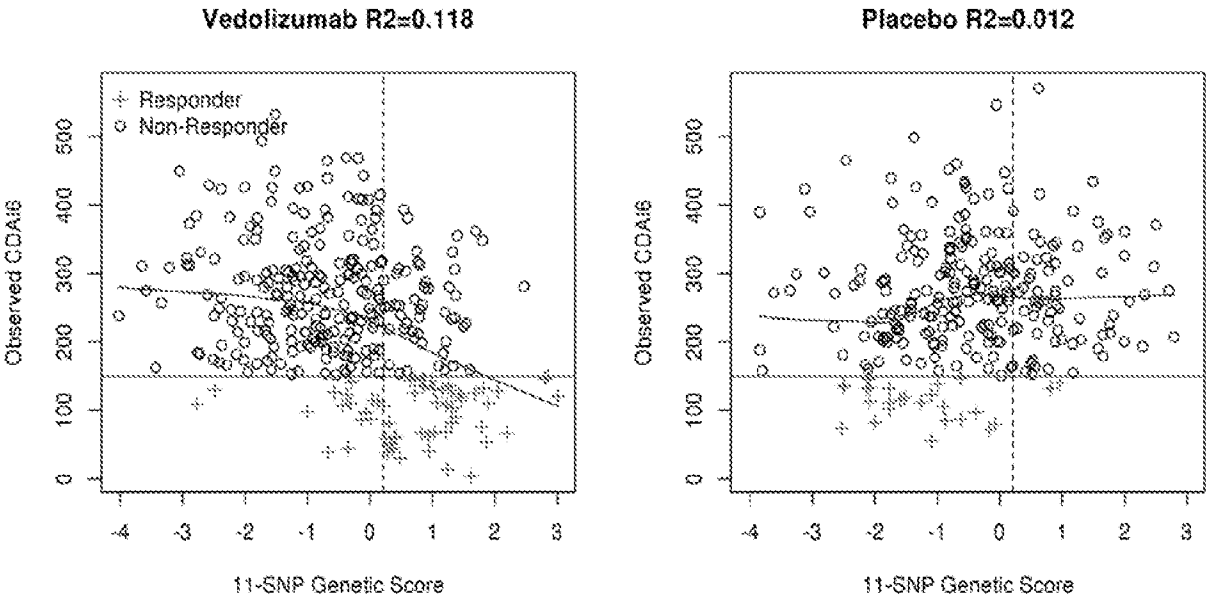
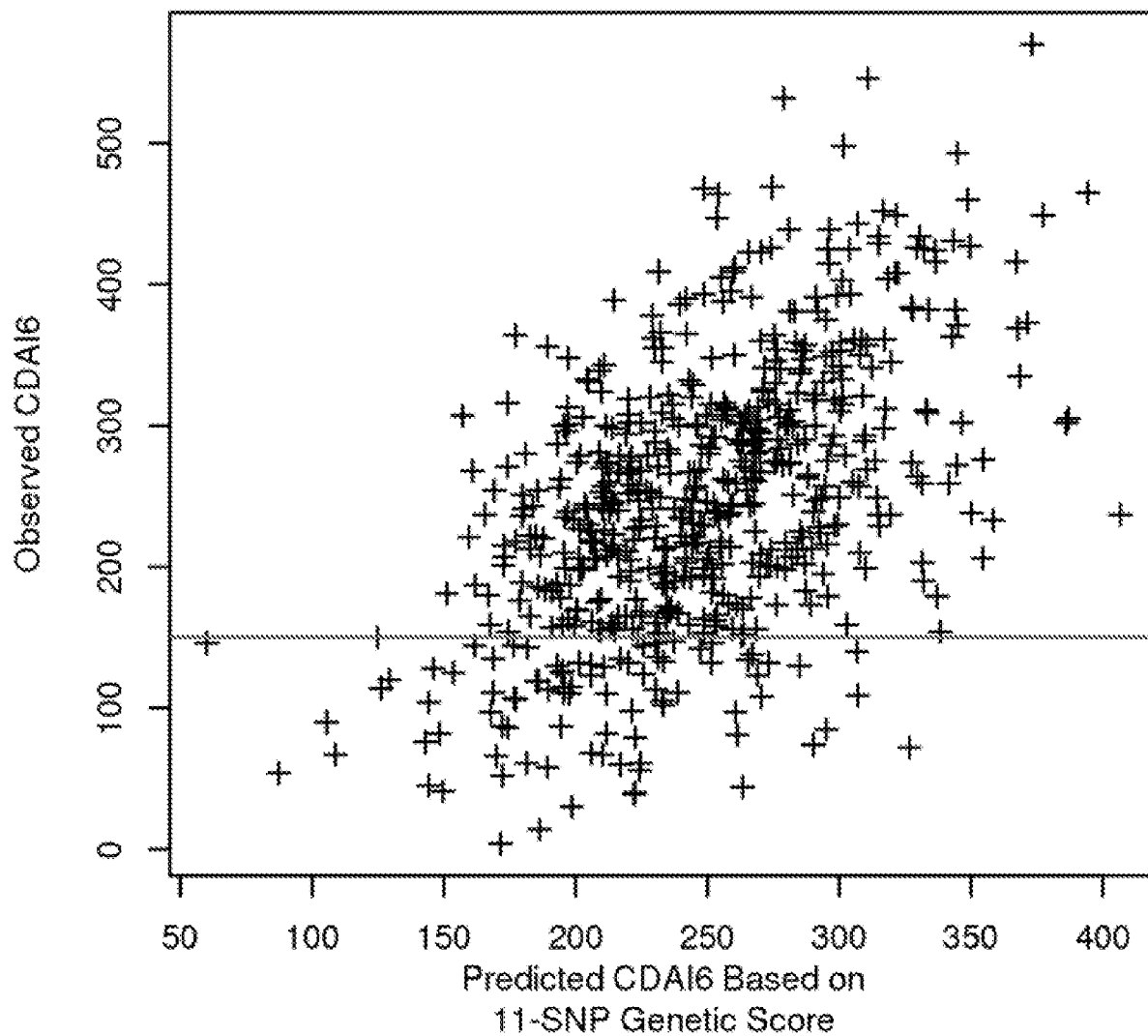
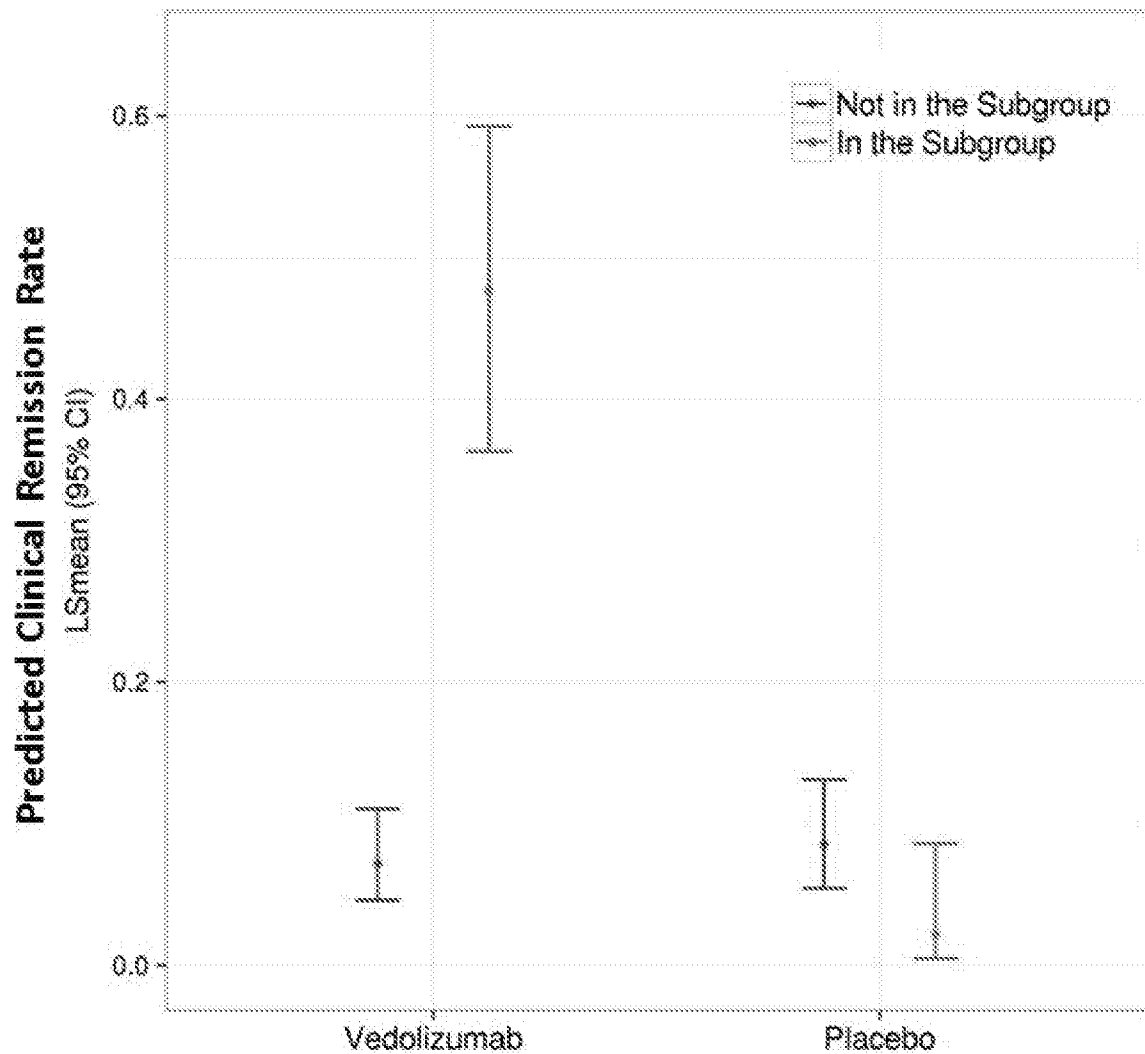


FIGURE 5G

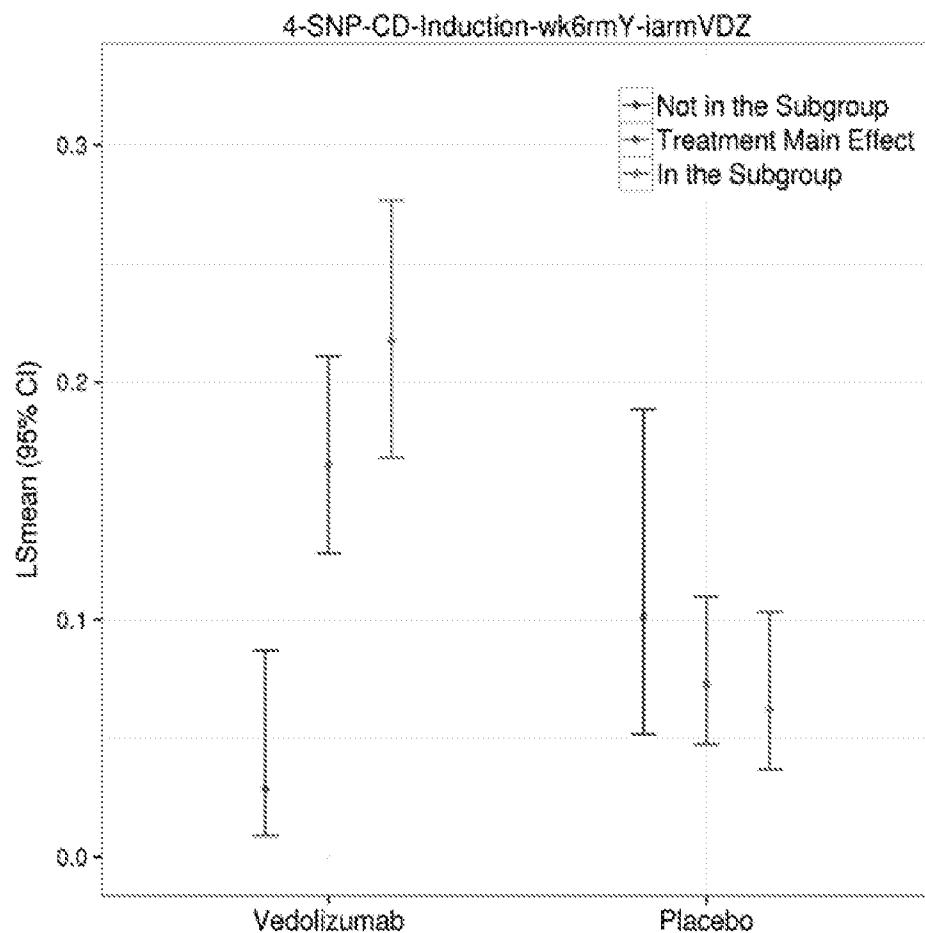
11-SNP Model: Observed vs. Predicted CDAI Score**Combined R²=0.278****FIGURE 5H**

8-SNP Model: Predicted Clinical Remission Rate

- Subgroup size: 24.12% (within Vedo arm)
- Tx OR w/in subgroup: 41.11 (9.03, 187.04)
- Tx OR outside subgroup: 0.83 (0.44, 1.57)
- Tx by subgroup interaction p-value: <0.0002
- Mean response rate in Tx arm within subgroup: 0.48 (0.36, 0.59)
- Mean response rate in Tx arm outside subgroup: 0.07 (0.05, 0.11)
- => 6.6 times more likely to respond

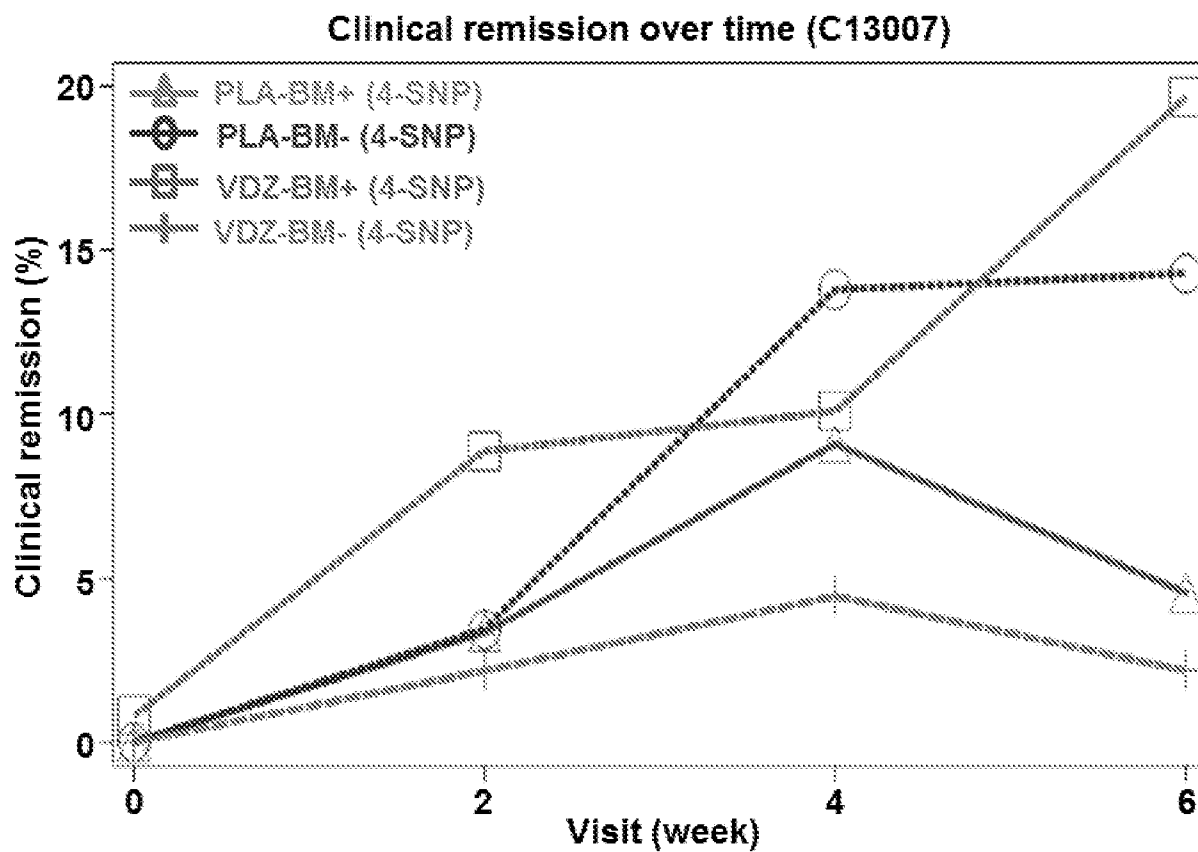
FIGURE 6

4-SNP Model: Clinical Remission of Crohn's Disease



- Subgroup size: 73.24% (within Vedo arm)
 - Tx OR in BM+: 4.20 (2.26,7.77)
 - Tx OR in BM-: 0.26 (0.07,1.01)
 - Tx by subgroup interaction p-value: **0.0010^a**
 - Tx RD w/in subgroup: 0.1533 (0.0889,0.2178)
 - Tx RD outside subgroup: -0.1040 (-0.1910,-0.0170)
 - Tx by subgroup Breslow p-value: **1.6e-05^b**
 - Mean response rate in BM+: 0.2176 (0.1683,0.2767)
 - Mean response rate in BM-: 0.0285 (0.0090,0.0870)
 - ~7.6 times more likely to respond
 - Pseudo R²: 0.135
- ^aBootstrap-adjusted P-value
^bUnadjusted P-value

FIGURE 7A



Note:

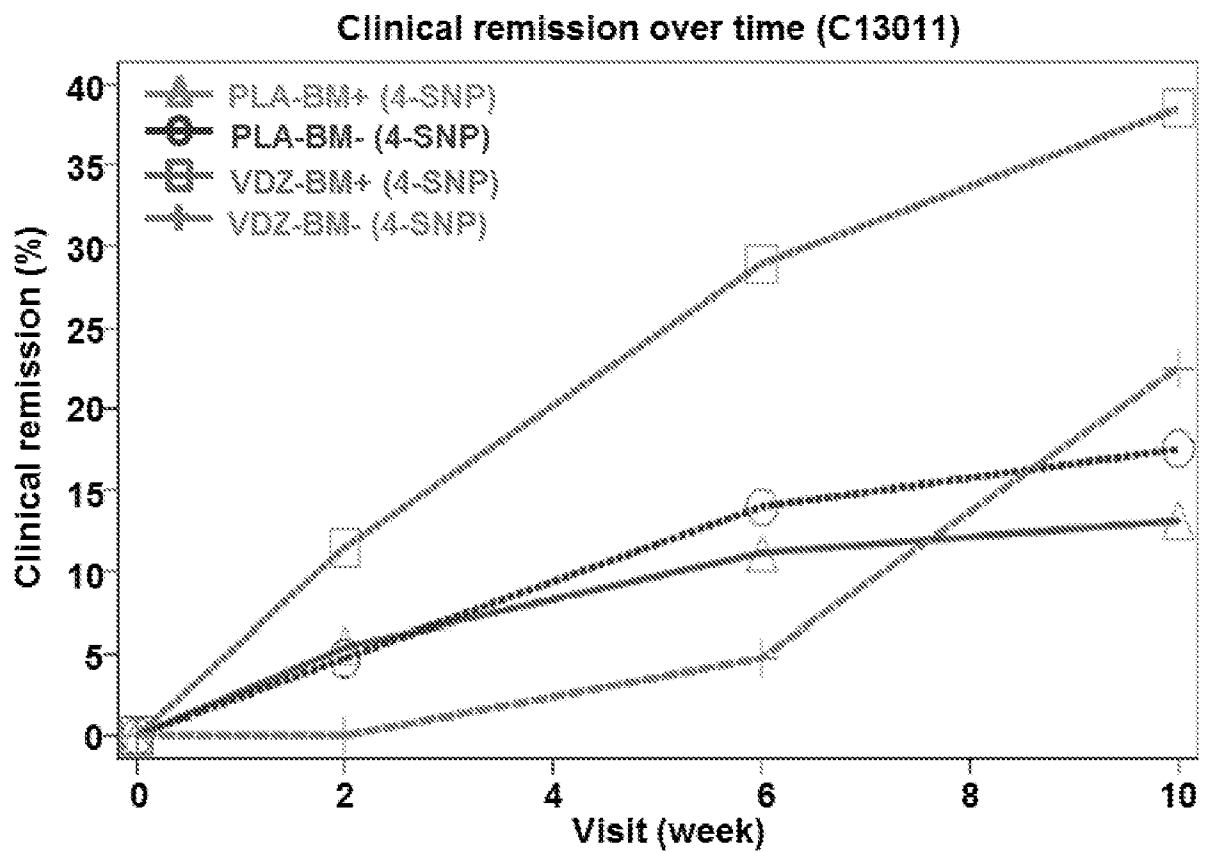
PLA BM+ at Week0 N=90, at Week6 N=88

PLA BM- at Week0 N=30, at Week6 N=28

VDZ BM+ at Week0 N=127, at Week6 N=117

VDZ BM- at Week0 N=46, at Week6 N=46

FIGURE 7B



Note:

PLA BM+ at Week0 N=111, at Week10 N=107

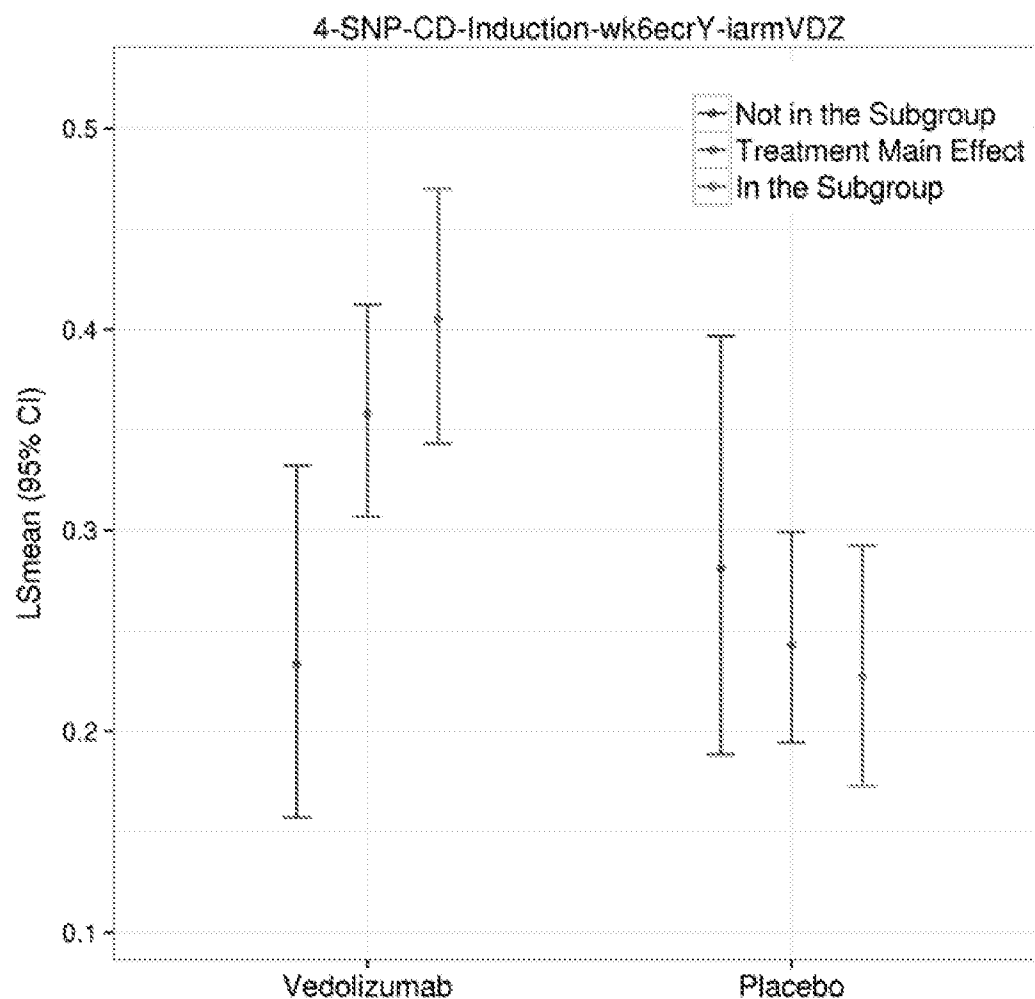
PLA BM- at Week0 N=43, at Week10 N=40

VDZ BM+ at Week0 N=122, at Week10 N=117

VDZ BM- at Week0 N=45, at Week10 N=40

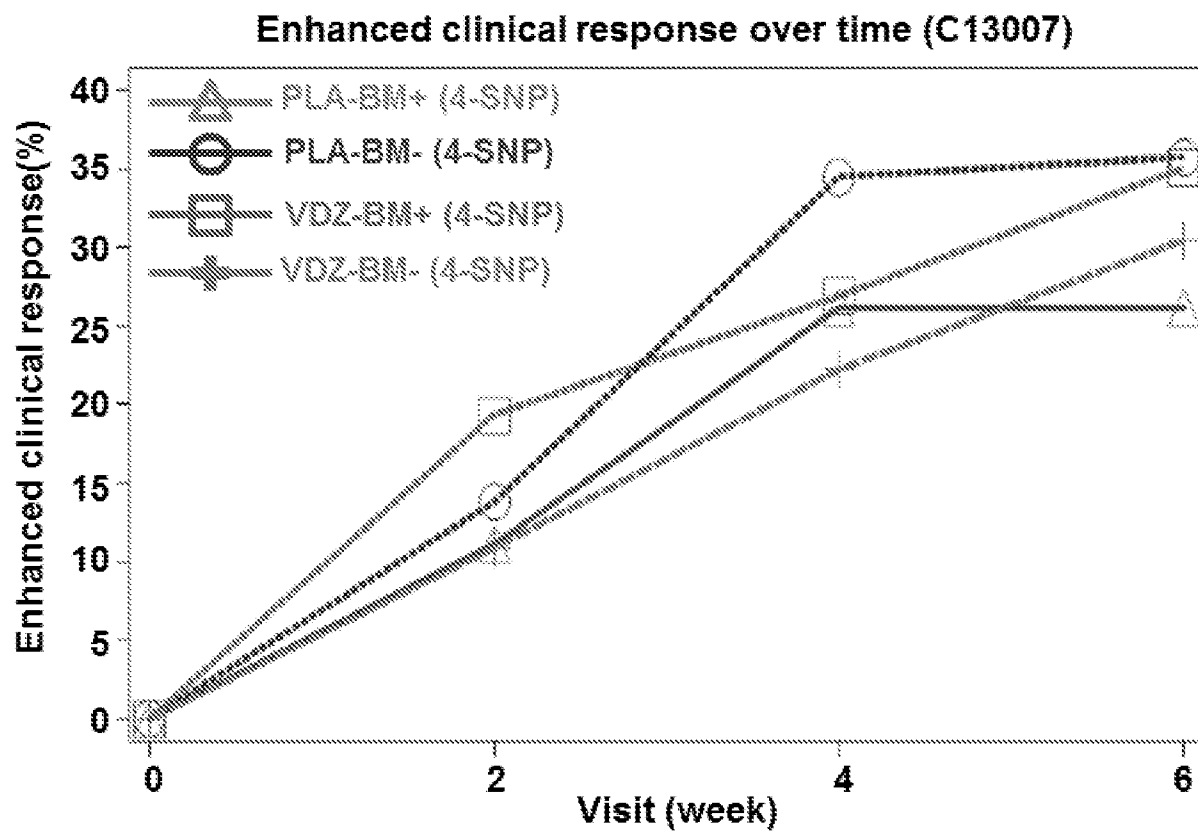
FIGURE 7C

4-SNP Model: Enhanced Clinical Response



- Subgroup size in Tx Arm: 73.24%
 - Tx OR BM⁺: 2.31 (1.50,3.56)
 - Tx OR BM⁻: 0.78 (0.38,1.58)
 - Tx by subgroup interaction p-value: **0.0100**
 - Tx RD BM⁺: 0.16 (0.08,0.25)
 - Tx RD BM⁻: -0.03 (-0.17,0.11)
 - Tx by subgroup Breslow p-value: **0.0272**
 - Mean response rate in Tx Arm BM⁺: 0.4050 (0.3432,0.4700)
 - Mean response rate in Tx Arm BM⁻: 0.2334 (0.1570,0.3324)
 - ~ **1.74 times more likely to respond**
- Pseudo R²: 0.073

FIGURE 7D



Note:

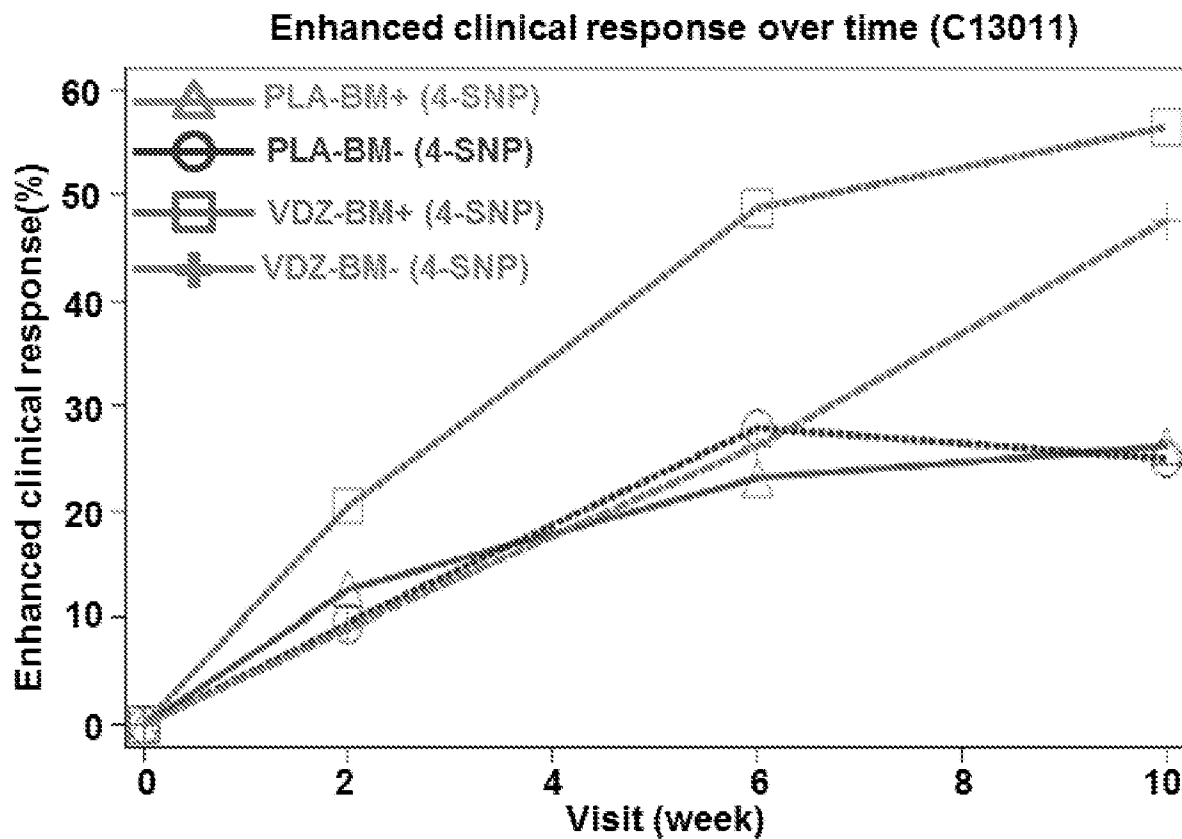
PLA BM+ at Week0 N=90, at Week6 N=88

PLA BM- at Week0 N=30, at Week6 N=28

VDZ BM+ at Week0 N=127, at Week6 N=117

VDZ BM- at Week0 N=46, at Week6 N=46

FIGURE 7E



Note:

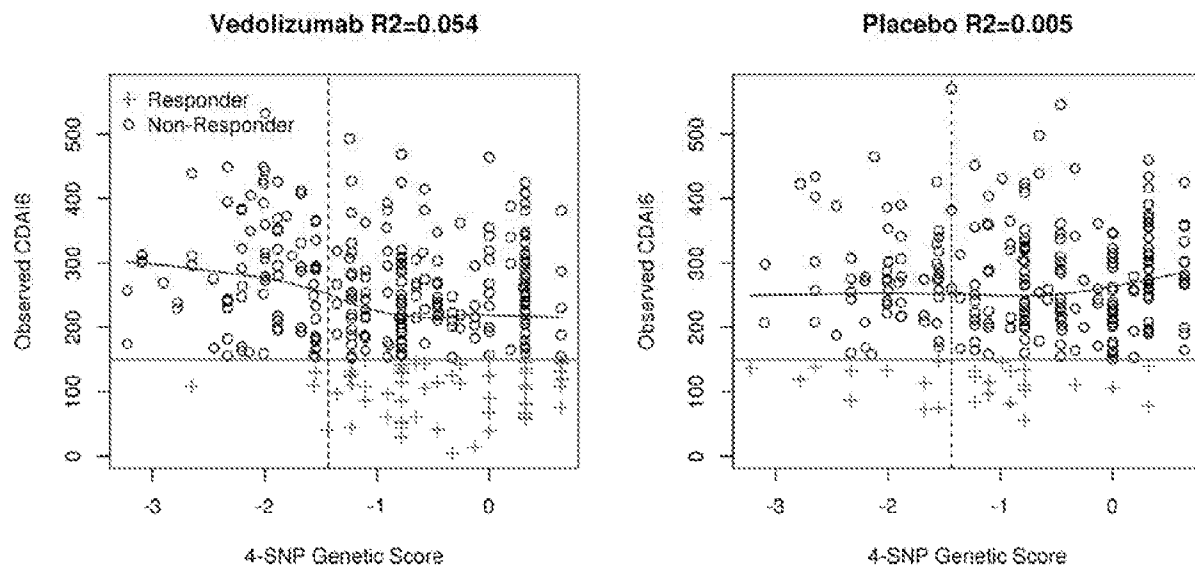
PLA BM+ at Week0 N=111, at Week10 N=107

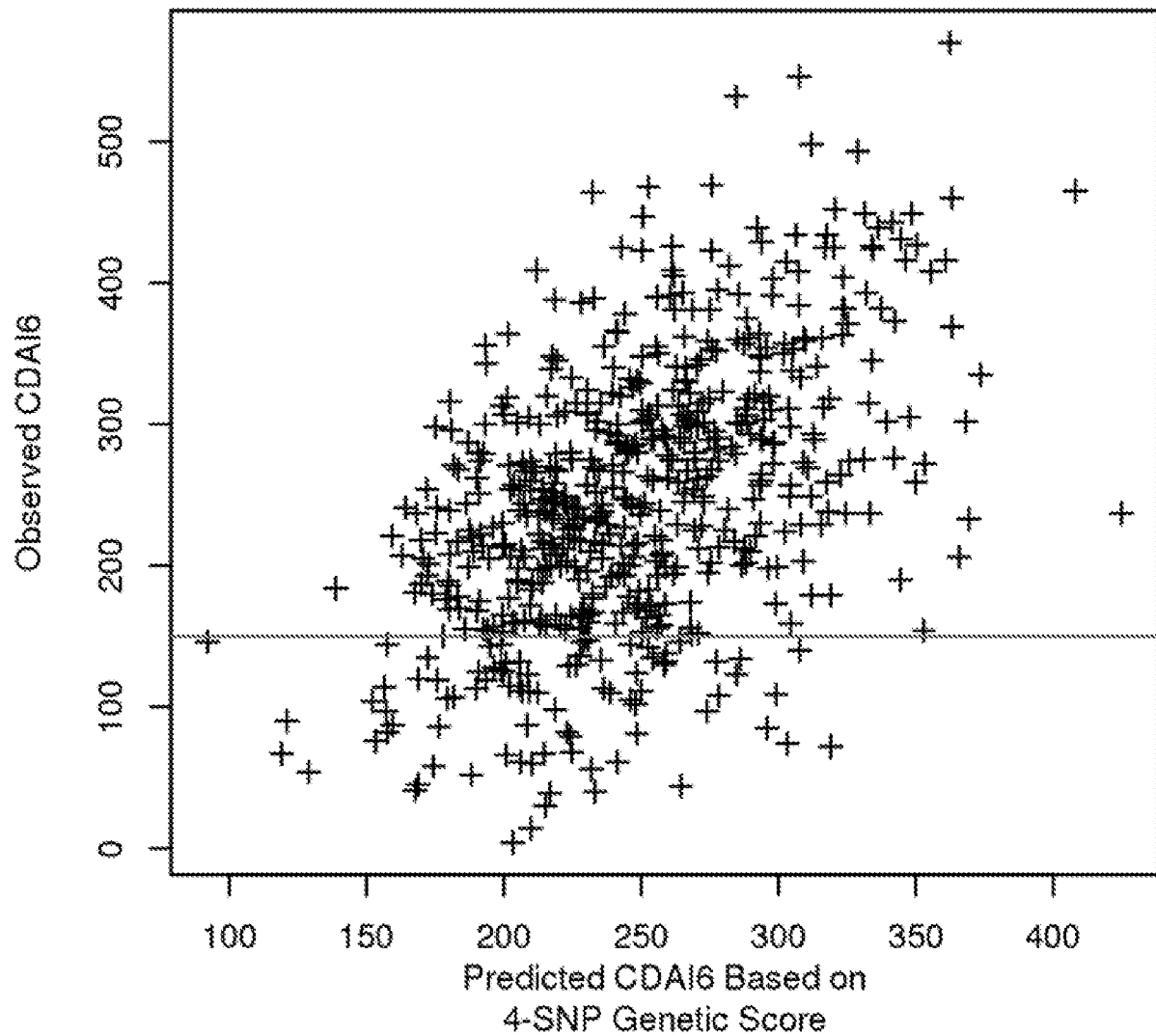
PLA BM- at Week0 N=43, at Week10 N=40

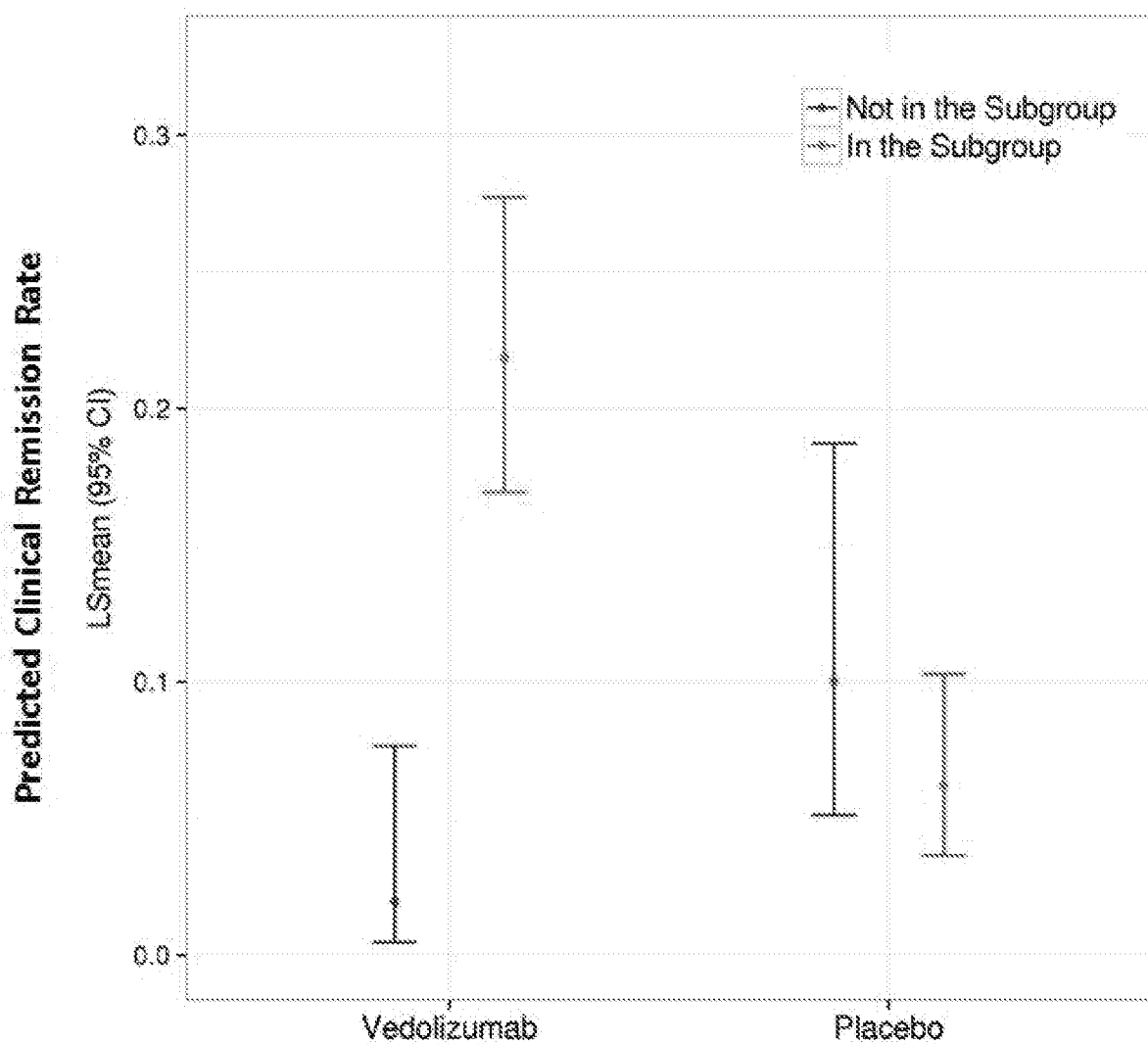
VDZ BM+ at Week0 N=122, at Week10 N=117

VDZ BM- at Week0 N=45, at Week10 N=40

FIGURE 7F

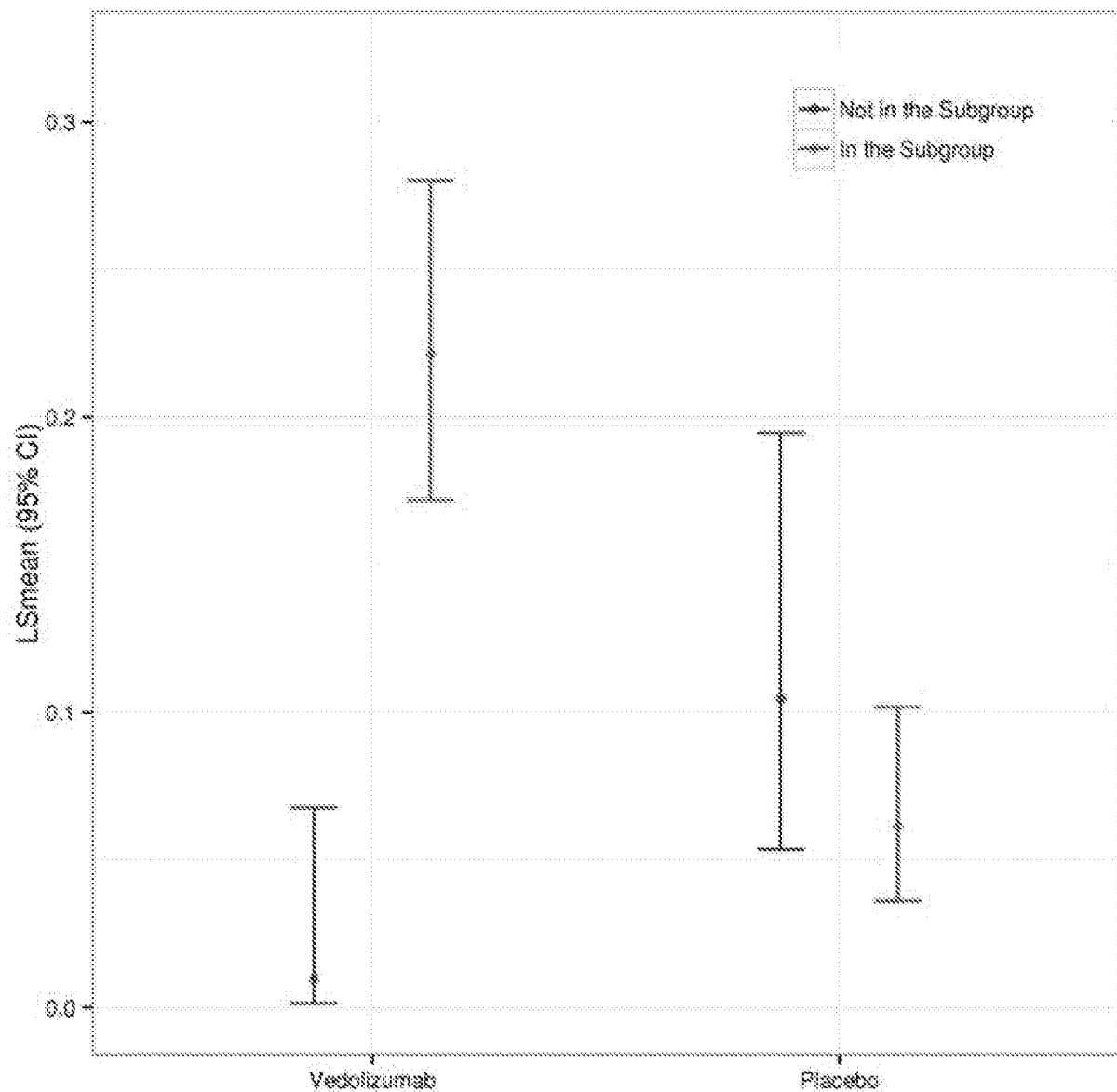
4-SNP Model: CDAI Score vs. Genetic Biomarker Score**FIGURE 7G**

4-SNP Model: Observed vs. Predicted CDAI Score**Combined $R^2=0.253$** **FIGURE 7H**

5-SNP Model: Clinical Remission of Crohn's Disease

- Subgroup size: 74.12% (within Vedo arm)
- Tx OR w/in subgroup: 4.24 (2.29,7.84)
Tx OR outside subgroup: 0.18 (0.04,0.87)
Tx by subgroup interaction p-value: 0.0004
Mean response rate in Tx arm within subgroup: 0.22 (0.17,0.28)
Mean response rate in Tx arm outside subgroup: 0.02 (0,0.08)
=> 11.2 times more likely to respond

FIGURE 8A

5-SNP Model: Clinical Remission of Crohn's Disease

- Subgroup size: 74.12% (within Vedo arm)
- Tx OR w/in subgroup: 4.36 (2.36, 8.06)
- Tx OR outside subgroup: 0.09 (0.01, 0.70)
- Tx by subgroup interaction bootstrap p-value for subgroup identification: <0.0002

FIGURE 8B

Distribution of Categorical Covariates in C13007 Cohorts

Variable	Cohort 1		Cohort 2 (n=572)	Overall (N=871)
	PLA (n=123)	VDZ (n=176)		
Prior treatment				
Missing	1 (0.81%)	1 (0.57%)	4 (0.70%)	6 (0.69%)
Anti-TNF	55 (44.72%)	84 (47.73%)	360 (62.94%)	499 (57.29%)
Corticosteroid	22 (17.89%)	29 (16.48%)	52 (9.09%)	103 (11.83%)
Immunomodulator	45 (36.59%)	62 (35.23%)	156 (27.27%)	263 (30.20%)
Sex				
Female	70 (56.91%)	90 (51.14%)	304 (53.15%)	464 (53.27%)
Male	53 (43.09%)	86 (48.86%)	268 (46.85%)	407 (46.73%)
Region				
Central Europe	28 (22.76%)	36 (20.45%)	116 (20.28%)	180 (20.67%)
Eastern Europe	12 (9.76%)	22 (12.50%)	19 (3.32%)	53 (6.08%)
North America	39 (31.71%)	51 (28.98%)	220 (38.46%)	310 (35.59%)
Northern Western Europe	21 (17.07%)	24 (13.64%)	164 (28.67%)	209 (24.00%)
Asia, Africa or Australia	23 (18.70%)	43 (24.43%)	53 (9.27%)	119 (13.66%)

- Cohort 2 seems to have
 - more anti-TNF failures
 - more Northern Americans and Northern, Western Europeans

FIGURE 9A

Distribution of Categorical Covariates in C13007 Cohorts (Cont.)

Variable	Cohort 1		Cohort 2 (n=572)	Overall (N=871)
	PLA (n=123)	VDZ (n=176)		
Age				
N	123	176	572	871
mean	38.27	36.41	35.73	36.23
SD	13.02	11.75	11.89	12.05
med	36.8	35	33.55	34.3
min	18.8	18.4	18.1	18.1
max	74.4	77.3	76.1	77.3
Baseline CDAI				
N	122	175	571	868
mean	323.73	327.68	324.09	324.76
SD	77.85	67.97	67.07	68.8
med	317.5	324	321	321
min	155	132	125	125
max	584	492	548	584

- Age and baseline CDAI distribution were similar across cohorts

FIGURE 9B

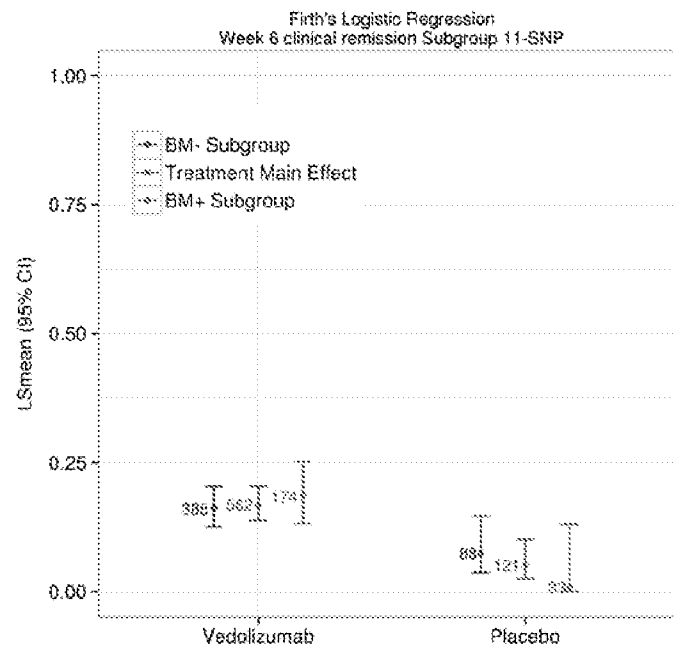
Summary of Response Rate in PGx Population

Variable (all at Week 6)	Cohort 1		Cohort 2 (n=572)	Overall (N=871)
	PLA (n=123)	VDZ (n=176)		
Clinical Response				
No	80 (65.04%)	100 (56.82%)	300 (52.45%)	480 (55.11%)
Yes	43 (34.96%)	76 (43.18%)	272 (47.55%)	391 (44.89%)
Enhanced Clinical Response				
No	90 (73.17%)	119 (67.61%)	381 (66.61%)	590 (67.74%)
Yes	33 (26.83%)	57 (32.39%)	191 (33.39%)	281 (32.26%)
Clinical Remission				
No	115 (93.50%)	151 (85.80%)	468 (81.82%)	734 (84.27%)
Yes	8 (6.50%)	25 (14.20%)	104 (18.18%)	137 (15.73%)

- Response rates for clinical response and clinical remission were higher in cohort 2 VDZ arm than those in cohort 1 VDZ arm

FIGURE 9C

LS Means Plot for 11-SNP Model on Clinical Remission at Week 6



BM+ subgroup size in Tx arm: 30.96%

BM+ subgroup size overall: 30.31%

Tx OR in BM+ subgroup: 24.98 (1.47, 423.89)

Tx OR in BM- subgroup: 2.37 (1.08, 5.21)

Subgroup interaction p-value: 0.0357

Pseudo R2: 0.106

Subgroup OR comparing BM+ and BM- in Tx arm: 1.17 (0.72, 1.88)

Mean response rate in Tx arm in BM+ subgroup: 0.185 (0.132, 0.252)

Mean response rate in Tx arm in BM- subgroup: 0.161 (0.126, 0.204)

Mean response rate in Tx arm overall: 0.169 (0.138, 0.204)

Within Tx arm:

1.146 times more likely to respond comparing BM+ and BM- subgroup

1.096 times more likely to respond comparing BM+ to overall

*All results based on logistic regression with Firth correction

FIGURE 10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/62651

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/395; C12Q 1/68; A61P 1/04; G06F 19/20 (2017.01)

CPC - C12Q 1/68, 1/6883, 1/6876; A61K 3/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/134585 A1 (TAKEDA PHARMACEUTICAL COMPANY LIMITED) September 11, 2015; page 7, lines 11-15; page 22, lines 13-22.	58, 122
Y	XU, et al. Psychometric Precision In Phenotype Definition Is A Useful Step In Molecular Genetic Investigation Of Psychiatric Disorders. Translational Psychiatry. 30 June 2015, Vol. 5, pages 1-8; doi:10.1038/tp.2015.86; table 1; page 3, second column, sixth paragraph.	58
Y	SRIVASTAVA, et al. Genetics Of Human Age Related Disorders. Advances in gerontology. January 2015, Vol. 28, pages 228-247; page 238, second column, first paragraph; page 238, second column, third paragraph.	122, 137
Y	WO 2015/153629 A1 (TEVA PHARMACEUTICAL INDUSTRIES LTD.) October 8, 2015; page 5, lines 20-23, 29; page 6, lines 1-3, page 15, lines 17-18.	137
A	US 2012/0282249 A1 (FOX, et al.) November 8, 2012; paragraphs [0023], [0027], [0135], [0184], [0271], [0272], [0290].	1-52, 59-60, 61/59-60, 86, 87, 88/86-87
A	EL-SALHY, et al. The Role Of The Neuropeptide Y (NPY) Family In The Pathophysiology Of Inflammatory Bowel Disease. Neuropeptides. 25 September 2015, Vol. 55, pages 137-144; doi: 10.1016/j.npep.2015.09.005; abstract; page 142, first column, second paragraph.	1-52
A	SANDBORN, et al. Vedolizumab As Induction And Maintenance Therapy For Crohn's Disease. The New England Journal of Medicine. 22 August 2013, Vol. 369, pages 711-721; DOI: 10.1056/NEJMoa1215739; abstract.	1-18, 59, 60, 61/59-60, 86, 87, 88/86-87

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

6 March 2017 (06.03.2017)

Date of mailing of the international search report

10 APR 2017

Name and mailing address of the ISA/

Mall Stop PCT, Attn: ISA/US, Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/62651

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0136720 A1 (MCGOVERN, et al.) May 30, 2013; paragraphs [0006], [0008], [0026].	19-52, 113, 114, 115/113-114, 116/113-114, 117/113-114, 118/117/113-114, 119, 120
A	US 2013/0012602 A1 (HARITUNIAN, et al.) January 10, 2013; paragraphs [0005], [0007], [0021].	19-52, 113, 114, 115/113-114, 116/113-114, 117/113-114, 118/117/113-114, 119, 120
A	WO 2011/088306 A1 (CEDARS-SINAI MEDICAL CENTER) July 21, 2011; page 2, third paragraph; page 4, sixth paragraph.	19-52
A	WO 03/066897 A2 (EVOTEC TECHNOLOGIES GMBH) August 14, 2003; page 12, third-fourth paragraphs; page 22, second paragraph.	53-57
A	US 2004/0241823 A1 (DIECKMANN, et al.) December 2, 2004; paragraphs [0046], [0054], [0055].	53-57

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/62651

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 62-85, 89-112, 129-136, 144-153
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.