Natalizumab (TYSABRI®) for CROHN'S DISEASE (CD)

BRIEFING BOOK

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EXECUTIVE SUMMARY

This Briefing Document has been prepared for members of the FDA's Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee to support the proposed indication for natalizumab (TYSABRI®): to induce and maintain response and remission, and eliminate corticosteroid use in patients with moderate to severely active Crohn's disease (CD) who have failed conventional therapy and have inflammation as evidenced by elevated C-reactive protein (CRP) or other objective marker. The full text of the indication statement is in Section 1.

Natalizumab is already approved for treatment of patients with relapsing forms of multiple sclerosis (MS) based on two placebo-controlled MS studies of two years' duration. Approval in MS included a comprehensive Risk Management Action Plan (RiskMAP) called the TYSABRI Outreach: Unified Commitment to Health (TOUCH) Prescribing Program, which has been successfully implemented for MS patients by the Sponsors. The Sponsors subsequently submitted a supplemental Biologics Licence Application (sBLA) for CD on 15 December 2006. This Briefing Document reviews all currently available clinical and safety data describing natalizumab and its use in patients with moderately to severely active CD.

Data presented in this document support the following statements:

- CD is a serious, progressive, disabling disease with a high unmet medical need for new and effective therapies.
- Natalizumab provides substantial clinical benefit to patients with moderately to severely active CD by inducing and maintaining clinical response and remission.
- Natalizumab is effective in patients who have been previously treated with other therapies used in CD, including inhibitors of TNF-α.
- Natalizumab is generally well tolerated but is associated with an increased risk of opportunistic infections (OI's), including progressive multifocal leukoencephalopathy (PML).
- The TYSABRI RiskMAP for MS patients, has been successfully implemented. Compliance with the program is excellent and there is a high degree of awareness of PML risk among patients and prescribers. From time of re-introduction in June 2006 until May 23, 2007, approximately 11,500 patients have received TYSABRI worldwide in the post-marketing setting, of which approximately 8,300 patients have been dosed in the US. Although long-term exposure data are limited, there have been no new confirmed cases of PML or other serious OI's reported.
- Once natalizumab is approved in CD, the current RiskMAP will be implemented for CD and adapted with minor modifications to accommodate differences in the

treatment and management of CD patients. This RiskMAP will educate CD patients and health-care providers and potentially minimize the risk of PML.

CROHN'S DISEASE

CD is a serious and disabling disease with a peak age of onset between 15 and 25 years of age, affecting patients in the prime of their lives. Nearly all Crohn's patients will eventually develop strictures or penetration complications (Cosnes *et al* 2002) and an estimated 70–90% of patients will require surgery for their condition at some time (Milsom 2005). Endoscopic recurrence occurs in most patients within one year of surgery and approximately 30% of patients require multiple surgeries (Kim *et al* 1997). Surgery itself carries a risk of mortality, and complications of multiple surgeries can lead to short-bowel syndrome (which may require the use of total parenteral nutrition), anastomotic leakage, sepsis, infertility and sexual dysfunction. Crohn's patients have higher rates of depression than the general population and an overall increased risk of mortality of approximately 50%, particularly those with more severe disease (Loftus 2006; Fuller-Thompson and Sulman 2006, Canavan 2007).

Treatment guidelines in the US (Hanauer and Sandborn 2002) recommend a step-wise approach to therapy. Patients with moderate to severe disease generally start therapy with systemic corticosteroids, followed by immunosuppressants (e.g. azathioprine) and finally with inhibitors of tumor necrosis factor alpha (TNF-α), i.e., infliximab and adalimumab, in those failing other therapies. Each therapy has limitations in terms of efficacy and has associated safety concerns, some of which are serious.

More than 40% of CD patients are non-responders to their initial TNF-α inhibitor therapy (Hanauer 2002; Humira® Prescribing Information). Furthermore, only approximately 40% of those that do initially respond to the TNF-α inhibitor therapy will maintain clinical response after a year of treatment and less than 30% of those that achieve remission remain in remission at one year without the use of corticosteroids (Remicade® Prescribing Information). Patients with CD who have received prior infliximab therapy or are intolerant to infliximab are capable of attaining remission with adalimumab. However, the magnitude of treatment effect is diminished relative to patients who have never been treated with infliximab (Humira Prescribing Information). A need for new therapies that maintain clinical response and remission in patients with active CD exists.

Summary of Major Efficacy and Safety Findings

Elan and Biogen Idec have conducted three Phase III studies evaluating the efficacy and safety of natalizumab in 1415 patients with moderately to severely active CD. These studies include two 3-month induction studies (CD301, CD307) and a 12-month maintenance study (CD303). All three pivotal studies evaluated 300 mg natalizumab administered every 4 weeks as an IV infusion over 1 hour, which is the currently approved dose regimen for MS.

The two induction studies (CD301 and CD307) were designed as 3-month, placebo-controlled trials. Both studies enrolled patients with moderately to severely active CD. In addition, patients entering CD307 were required to have elevated CRP, defined as CRP greater than the upper limit of normal [ULN] at screening.

- The primary endpoint for CD301 was a comparison of the proportion of patients in response (≥70-point decrease in Crohn's Disease Activity Index [CDAI] score from baseline) at Week 10: 56% of natalizumab-treated patients were in response *vs* 49% of placebo patients (p=0.051).

- Secondary endpoints are presented in Table 1. Remission at Week 10 was to be a co-primary outcome if statistical significance had been reached for the primary outcome. Trends were seen on 3 of the secondary outcomes (response at Week 2, remission at Week 10 using 100 point improvement in CDAI, and change in IBDQ at Week 10).

Table 1 CD301: Secondary Endpoints

Endpoint	Natalizumab *vs* Placebo	p-value
Proportion of patients in remission at Week 10	37% *vs* 30%	0.124
Proportion of patients in remission[1] at Week 4	23% *vs* 19%	0.351
Proportion of patients in response at Week 2	40% *vs* 33%	0.060
Proportion of patients with >100-point improvement in CDAI score at Week 10	49% *vs* 41%	0.046
Change from baseline in IBDQ at Week 10	+35 *vs* +28	0.037

[1] Remission was defined as a CDAI score <150

- Further post-hoc analysis revealed that treatment effect was more apparent in those with elevated CRP, an objective marker of inflammation. To test this hypothesis, elevated CRP was an entry criterion for the second induction study, CD307.

- The primary endpoint for CD307 was a comparison between treatment groups of the proportion of patients in response at both Weeks 8 and 12. The choice of dual time-point was to ensure response was durable. A significantly higher proportion of natalizumab-treated patients than placebo patients experienced a clinical response (48% *vs* 32%; p<0.001) at both Weeks 8 and 12.

All prospectively defined secondary endpoints were met (Table 2):

Table 2 CD307: Secondary Endpoints

Endpoint	Natalizumab *vs* Placebo	p-value
Proportion of patients in remission at both Weeks 8 and 12	26% *vs* 16%	0.002
Proportion of patients in response at Week 12	60% *vs* 44%	<0.001
Proportion of patients in remission at Week 12	37% *vs* 25%	0.001

- In addition, at every timepoint assessed natalizumab showed a significant treatment effect compared to placebo for both response and remission, and early onset of clinical benefit was demonstrated with significant treatment effect for both response and remission noted at Week 4.

- The elevated CRP subpopulation (>70% of the Intent-to-Treat [ITT] population) in the earlier CD301 study was also analyzed according to the timepoint and analysis rules used to analyze the CD307 ITT Population. At both Weeks 8 and 12 of CD301, there was a significant treatment difference for response (49% natalizumab *vs* 34% placebo; p=0.002) and for remission (29% *vs* 19%; p=0.041). The treatment difference was similar to that seen in CD307.

Patients in response after 3 months of induction therapy in CD301 were re-randomized to receive either natalizumab or placebo administered monthly for an additional 12 months (i.e., through to Month 15) in CD303:

- The primary outcome for CD303 was a comparison of patients who maintained clinical response at every monthly assessment through to the primary endpoint of Month 6 in CD303 (Month 9 of continuing treatment involving CD301 and CD303). The proportion sustaining response was 61% for natalizumab *vs* 28% for placebo (p<0.001). Similar results were seen for sustained remission through to Month 6 (Month 9 of continuing treatment), achieved by 44% of natalizumab patients compared with 26% of placebo patients (p=0.003).
- All CD303 secondary endpoints (Table 3) achieved statistical significance. More than twice the proportion of patients in the natalizumab group compared with placebo sustained response through to Month 15 and sustained remission through to Month 15 of treatment. Similarly, more than twice the proportion of natalizumab patients compared with placebo discontinued steroids at Month 9, or remained in remission and discontinued steroids at Month 9. Similar results were obtained at Month 15. In addition, pre-specified tertiary outcomes - health-related quality of life (HRQoL), as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ) (and SF-36) - showed significant improvements over placebo.

Table 3 CD303: Secondary Endpoints

Endpoint	Outcome (Natalizumab vs Placebo)	p-value
Proportion of patients in sustained response through to Month 15	54% *vs* 20%	<0.001
Proportion of patients in sustained remission through to Month 15	39% *vs* 15%	<0.001
Time to loss of response (comparison of the distribution)	Median time: not determined[1] vs 86 days	<0.001
Time to loss of remission (comparison of the distribution)	Median time: 137 days *vs* 59 days	<0.001
Mean change from CD301 baseline in IBDQ score at Month 9	+53 *vs* +39	<0.001
Proportion of patients not taking oral steroids at Month 9	58% *vs*28%	<0.001
Proportion of patients in remission and not taking oral steroids at Month 9	45% *vs* 22%	0.014

[1] The median time to loss of response in the natalizumab group could not be determined as most patients remained in response through to Month 15

The safety of natalizumab was analyzed in a total of 3,884 natalizumab-treated patients (1,563 in clinical trials in CD), resulting in 4,659 patient-years of natalizumab exposure. In short-term placebo-controlled trials in active CD, 1,182 patients have received natalizumab. The integrated analyses of safety from trials of natalizumab in CD demonstrate the following:

- Treatment with natalizumab was generally well tolerated.
- The incidence of common and serious adverse events was similar in natalizumab-treated patients and placebo controls.
- The incidence of hypersensitivity reactions with natalizumab treatment was 3.5%. Two CD patients (0.1%) experienced a serious systemic hypersensitivity reaction, both of which resolved without sequelae.
- The overall incidence and rate of common and serious infections were similar in natalizumab-treated patients and control patients.
- Serious OI's, including PML, occurred with natalizumab treatment in 0.3% of CD patients.
- Three cases of PML were reported, one in a CD patient and two in MS patients. These cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants. To potentially minimize the risk of OI's, including PML, the proposed labeling warns against the use of natalizumab either in

immuncompromised patients or concomitant use with chronic immunosuppressant or other immunomodulatory therapies.

- The rate of malignancies in the placebo-controlled CD experience is higher in natalizumab-treated patients compared with placebo; however the number of events is small. The rate of malignancies in the pooled MS and CD placebo-controlled trials is similar for natalizumab- and placebo-treated patients.
- Approximately 5% of CD patients who received natalizumab in clinical studies developed persistent anti-natalizumab antibodies, defined as antibodies detected on more than one sample, which were associated with reduced efficacy and a higher incidence of hypersensitivity reactions. The Sponsors recommend that prescribers should consider the overall benefits and risks of natalizumab in a patient with persistent antibodies.

Summary of Risk Minimization Action Plan (RiskMAP)

Biogen Idec and Elan Pharmaceuticals, in consultation with the FDA[1], have successfully implemented a comprehensive risk management plan to accompany use of natalizumab in MS patients, consisting of both risk assessment and risk minimization features. This plan is called the TOUCH (TYSABRI Outreach: Unified Commitment to Health) Prescribing Program.

The MS TOUCH program is designed to promote informed benefit-risk decisions between prescribers and patients regarding the use of natalizumab in relapsing MS, to minimize morbidity and mortality due to PML through early detection with clinical vigilance, and to minimize the risk of PML by treating patients who are not immunocompromised and, consistent with the Prescribing Information (PI), warning against concurrent use with antineoplastics, immunosuppressants or immunomodulators. In addition, the existing plan seeks to determine the incidence and risk factors for PML and other serious OI's in patients treated with natalizumab, as well as the overall safety of natalizumab in the clinical practice setting.

The MS TOUCH Prescribing Program features, among other things:

- Mandatory enrollment of all prescribers and patients into the TOUCH Prescribing Program, a registry that provides diligent safety surveillance and systematic tracking of all patients.
- Mandatory training and enrollment of all infusion sites and all central pharmacies affiliated with authorized infusion sites into the TOUCH Prescribing Program.

[1] *See* FDA, Guidance for Industry -- Development and Use of Risk Minimization Action Plans (March 2005).

- Controlled distribution system for TYSABRI so that TYSABRI is delivered to and administered only in authorized infusion sites.
- Mandatory completion of the Pre-Infusion Patient Checklist and distribution of the Medication Guide to each patient prior to each monthly TYSABRI dose.
- Real-time submission of Pre-Infusion Patient Checklists to Biogen Idec to monitor infusion site compliance and to track TYSABRI dosing on a patient-specific basis.
- Mandatory prescriber re-authorization of TYSABRI dosing for each patient every 6 months.
- At the heart of the TOUCH Prescribing Program is an integrated, computerized, validated database that captures enrollment, patient tracking, and drug distribution data.

The MS TOUCH Prescribing Program has been successfully implemented. Since the re-introduction of natalizumab in June 2006 until 23 May 2007, approximately 11,500 patients have been treated with natalizumab worldwide, of which approximately 8,300 patients have been treated in the US. Approximately 1,750 physicians have enrolled patients into the program and 1,750 infusion sites have been trained and authorized. Compliance with the program is excellent. Since the re-introduction in June 2006 until 23 May 2007, 99.9% of natalizumab infusions have been administered to patients enrolled in the program. 38,898 Pre-Infusion Patient Checklists were expected, of which 99.9% were received by the Sponsors. 2740 re-authorization forms were expected, of which 99.6% were received. 96.8% of patients received no concurrent immunomodulatory or immunosuppressant therapies. The Sponsors sent 10,125 shipments of TYSABRI, of which 99.9% were sent to authorized infusion sites. Surveys of enrolled prescribers and infusion nurses indicate high levels of PML awareness and understanding of the program requirements. Since the re-introduction, no new confirmed cases of PML or other serious OI's have been reported worldwide.

Upon approval of natalizumab in CD, a similar program to the TOUCH Prescribing Program will be implemented for CD patients (CD-TOUCH). While the goals and objectives of the TOUCH Prescribing Program will be the same for MS and CD, it is proposed that the methods of the TYSABRI RiskMAP for MS patients be adapted for Crohn's patients with minor modifications to accommodate differences in the treatment and management of patients with CD. These changes include alteration of appropriate patient, physician and infusion site forms and communication tools to include and substitute (as appropriate) information on CD and use of natalizumab in CD.

CONCLUSIONS

CD is a serious and disabling chronic inflammatory disease for which there exists a substantial unmet need for new and effective treatments, particularly for patients with active disease who have failed conventional therapy. Results from the three pivotal studies demonstrate statistically significant, and clinically meaningful efficacy in

inducing and maintaining clinical response and remission in patients with active CD. These results are supplemented by the ability of natalizumab therapy to reduce the need for corticosteroid therapy and to improve the patient's quality of life. The major safety findings are the uncommon occurrence of serious OI's, including PML and the occurrence of serious systemic hypersensitivity reactions in 0.1% of patients. A RiskMAP has been successfully implemented in patients with MS and the Sponsors will adapt this plan for use in patients with CD with minor modifications. In summary, the clinical data demonstrate a favorable benefit to risk profile of natalizumab as treatment of patients with moderately to severely active CD with evidence of active inflammation.

1 INTRODUCTION AND BACKGROUND

This Briefing Document has been prepared for members of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee to provide efficacy and safety data describing the benefits and risks of TYSABRI® (natalizumab) as treatment for patients with Crohn's disease (CD).

- Natalizumab was approved for treatment of patients with relapsing forms of multiple sclerosis (MS) on 23 November 2004 after priority review of 1-year data from two ongoing 2-year studies. Accelerated approval in MS was conditional on providing confirmatory 2-year results. These data demonstrated strong clinical evidence of efficacy (67% relative reduction in relapse rate, 42% relative reduction in risk of disability progression).

- Following the recognition of two cases of progressive multifocal leukoencephalopathy (PML), the Sponsor and FDA agreed that commercialization and dosing in clinical trials should be suspended on 28 February 2005. A third PML case was subsequently identified retrospectively, in a CD patient, during a review of the complete safety database.

- The Sponsor conducted a formal re-evaluation of over 3,000 CD, MS and rheumatoid arthritis (RA) patients who received natalizumab in clinical studies and approximately 7,000 MS patients in the commercial setting. No additional cases of PML were identified in these patients.

- A supplemental BLA (sBLA) that included the 2-year safety and efficacy MS results was submitted in September 2005.

- Following a positive recommendation from the Peripheral & Central Nervous System Drugs Advisory Committee, FDA approval for the reintroduction of natalizumab in MS was granted in the US in June 2006.

- An sBLA for CD was submitted on 15 December 2006, that included data from three Phase III efficacy and safety trials of Natalizumab: two 3-month induction studies in patients with moderately to severely active CD and a 12-month maintenance study following one of the induction studies.

This Briefing Document presents a clinical overview of CD, including a description of currently available therapies (the remainder of Section 1); the clinical data demonstrating the efficacy of natalizumab as treatment for patients with CD (Section 2); the clinical trial safety data following over two years of exposure to natalizumab, results of the post-dose suspension safety evaluation, as well as the post-marketing safety data (Section 3); the Sponsor's RiskMAP (Section 4) designed to both minimize and further assess the risk of PML and other serious OI's; and finally, the benefits and risks of natalizumab as treatment for patients with CD (Section 5).

Based upon data provided, the Sponsor believes that natalizumab (TYSABRI®) has a benefit-risk profile that supports approval for the following indication for CD:

TYSABRI® is indicated for inducing and maintaining sustained response and remission, and eliminating corticosteroid use in patients with moderately to severely active Crohn's disease with inflammation, as evidenced by elevated CRP level or other objective marker.

Because TYSABRI® increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies.

The Sponsor also proposes to prominently warn against concurrent use with certain other CD treatments (i.e., immunosuppressants, immunomodulators) and against use in immunocompromised individuals as follows:

Ordinarily, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI®.

1.1 CROHN'S DISEASE

1.1.1 Clinical Course of CD

Crohn's disease (CD) is characterized by chronic inflammation of all layers of the bowel wall, potentially affecting any segment of the GI tract. The most common sites are the distal small intestine and proximal colon, followed by the small intestine alone and then by the colon alone. The precise cause of CD is unknown, but it is believed to be an autoimmune disease ultimately due to a combination of genetic, environmental and immunologic factors (MacDonald and Monteleone 2005). In North America, the incidence of the disease is estimated to be between 3.1 and 14.6 cases per 100,000 person-years, with between 10,000 and 47,000 new cases of CD diagnosed annually. Based on a prevalence of 199 cases per 100,000 persons, it is estimated that over 630,000 people in North America have CD (Loftus 2004). The peak age of disease onset is between 15 and 25 years (Russel and Stockbrugger 1996), such that most patients are affected for many decades. Recent data suggest that CD is being diagnosed at increasingly younger age groups (Diefenbach and Breuer, 2006).

CD is a chronic, frequently debilitating inflammatory condition and one-half to two-thirds of patients, at any given time, have disease activity categorized as ranging from moderate to severe. The typical symptoms of active severe CD include abdominal pain, fever, malaise, anorexia, weight loss, and frequent diarrhea with rectal bleeding. On external examination the patient is often thin, febrile, and may be fluid depleted. In patients developing bowel perforation, further deterioration is usually obvious with sudden worsening of abdominal pain, distension, fever, tachycardia, sepsis and shock.

Nearly 90% of all Crohn's patients will eventually develop a stricturing or penetrating complication (Cosnes *et al* 2002). Surgery is often necessary for Crohn's-related complications, and an estimated 70–90% of Crohn's patients will require surgery at some point in the course of their disease (Milsom 2005). Although most surgical episodes are elective, some emergency surgical procedures are carried out, with morbidity rates of up to 50% and mortality rates of 11% (Furst and Schildberg 1998). The risk of postoperative complications is further increased in patients on concomitant corticosteroids. Although surgical outcomes can be successful, endoscopic recurrence occurs in most patients within one year, and approximately 30% of patients require multiple surgeries (Kim *et al* 1997). Surgery itself carries a risk of mortality, and complications of multiple surgeries can lead to short-bowel syndrome (which may lead to the use of total parenteral nutrition), anastomotic leakage, sepsis, infertility, and sexual dysfunction. This represents a significant disease burden in a population of mainly young adults.

Despite the increased use of immunosuppressants over time, the incidence of surgery and permanent stoma, although delayed, has not changed (Cosnes *et al* 2005). In large studies, failure of medical therapy has been cited as the reason for resection in anywhere from 16% to 68% of patients and obstruction in 22% to 45% (Penner *et al* 2005). Not only is there a mortality risk associated with surgery, there are often limitations and complications of surgery, independent of the risk associated with CD alone. Along with the significant negative effects of active disease on patients' HRQoL these observations illustrate that CD is a severely debilitating chronic and progressive disease.

In addition to the morbidity associated with disease, there is a 50% increase in standardized mortality rates in Crohn's patients relative to the normal population (Canavan 2007).

In the US, the direct cost of CD was estimated to be $708 million in 1998. Adjusting for increases in disease prevalence and annual health care inflation produces a 2006 direct cost estimate of $1.37 billion (Sandler *et al* 2002; US Department of Labor 2007; Sands *et al* 2006). This does not include the cost to patients and society from productivity losses due to absenteeism and poorer work performance when on the job. Because the disease afflicts patients during their prime wage-earning years, this impact can be substantial. Among a sample of 342 U.S. patients, 38% reported that CD had at some point kept them from being employed either full-time or part-time. In addition, among those who were currently employed, 24% of their scheduled work hours in the previous week had been lost because of their disease. Effective treatment has been shown to be associated with the ability to return to the workforce. Unemployed CD patients with moderately to severely active CD who went into remission at one-year post-treatment initiation were nearly twice as likely to be employed than those who did not achieve remission (31% *vs* 16%) (Lichtenstein *et al* 2004).

A cumulative effect of the factors described above is the substantial impairment on Crohn's patients' health related quality of life (HRQoL)(Blondel-Kucharski *et al* 2001; Bernklev *et al* 2005; Casellas *et al* 2001; Farmer *et al* 1992). Rates of depression, including rates of suicidal ideation, are higher in patients with CD than in the general population (Fuller-Thompson and Sulman 2006). Disease-related symptoms, adverse reactions associated with the use of conventional therapies, psychological factors related to the uncertainty of the course of disease, reduced labor force participation and fear of surgery, particularly ostomy, with its associated complications, all culminate in a disease with a significant burden of illness for patients, relatives and society (Canavan *et al* 2006; Marri and Buchman 2005; Boonen *et al* 2002). It is not surprising that CD has been shown to result in a degree of impairment of HRQoL that is as least as severe as other debilitating diseases such as diabetes mellitus, rheumatoid arthritis, ulcerative colitis and severe angina (Ware 1993; Borgaonkar and Irvine 2000; Gregor *et al* 1997).

1.1.2 Pathophysiology of CD

CD is currently presumed to result from a combination of genetic (e.g., CARD15/NOD2) and environmental factors (e.g., smoking) conferring risk of disease and leading to an inflammatory response. Defects in innate immune response may also play a role in the development of CD. In addition, the contribution of intestinal microflora is of increasing interest regarding disease etiology (Korzenik and Podolsky 2006).

Chronic inflammation is a hallmark of CD. Therapeutic strategies for the disease generally aim to interrupt cytokine activity or, as with natalizumab, to block leukocyte migration to sites of inflammation. Increased leukocyte trafficking across the vascular endothelial lining into the parenchyma of the gastrointestinal (GI) tract is believed to play a key role in the pathogenesis of CD.

The interaction of both the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins, expressed at high levels on all circulating leukocytes except neutrophils, and on hematopoietic progenitor cells, with their respective endothelial receptors VCAM-1 and MadCAM-1 are important contributors to this chronic inflammation (see Section 1.4).

1.1.3 Outcome Measures for CD

The CDAI score is the most commonly used measure in clinical studies evaluating the efficacy of new therapies in CD patients with predominantly inflammatory disease (Sandborn *et al* 2002). This index is primarily based on a subject-completed questionnaire. Reduction by either 70 or 100 points from baseline CDAI score has been used to define clinical response in studies evaluating new therapies for patients with CD. Remission is defined as a CDAI score <150.

Although the CDAI score is an indicator of a subject's symptoms, it does not distinguish between symptoms due to CD as opposed to similar symptoms due to other causes. For most patients with CD who present with moderate to severe symptoms of their disease,

the symptoms are caused by active inflammation of the bowel tissue. However, a subset of patients may experience similar symptoms, including diarrhea, abdominal pain, and weight loss, due to etiologies other than active inflammation e.g., bile salt diarrhea, bacterial overgrowth syndrome, short bowel syndrome and functional bowel disease.

C-reactive protein (CRP) enables identification of patients with CD symptoms who in addition have objective evidence of active inflammatory disease (Sands and Ooi 2005). Thus, the second induction study (CD307) included an entry criterion for patients to have an elevated CRP level above the upper limit of normal (ULN) (i.e., >2.87 mg/L) in order to select for patients with an inflammatory component to the CD activity (see Section 2.1). Analyses using higher CRP cut-off values disclosed no better discriminant level of CRP than the ULN. Reduction of inflammation, as defined by a decrease in CRP, albumin or platelets over time, was assessed in the natalizumab CD program.

HRQoL was measured within the natalizumab clinical trial program to obtain the patient's perspective on symptom burden and the effect of treatment on social and emotional well-being. The Inflammatory Bowel Disease Questionnaire (IBDQ) is a validated disease-specific measure designed to assess the quality of life of patients with IBD (Irvine *et al* 1994). It has been widely used in clinical studies evaluating the effect of new CD therapies on HRQoL. The total IBDQ score ranges from 32 to 224, with higher scores indicating better HRQoL. It is comprised of four component scales (bowel symptoms, systemic symptoms, emotional function and social function). A total IBDQ score >170 is associated with clinical remission (Irvine *et al* 1994). The Short-Form 36 Health Survey Questionnaire (SF-36) is a validated, general quality of life measure containing 36 questions, which assesses health status (Brazier *et al* 1992). Data from the SF-36 can be used to calculate two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These summary scales are computed such that a mean score of 50 (SD=10) corresponds to that of the US general population.

1.2 CURRENT THERAPY FOR CD

The current approach to the treatment of CD focuses on four major objectives: To alleviate symptoms, induce response and remission, maintain response and remission and to achieve these goals without significant toxicity. Some of the therapies currently available are intended for short-term use in order to induce remission, others are used as long-term maintenance therapy, but none of the currently available therapies effectively satisfy all treatment objectives stated above. Furthermore none of the older therapies currently used have been approved for treatment of CD in the USA.

Treatment guidelines in the USA (Hanauer and Sandborn 2001) recommend the following step-wise approach to therapy: A patient may initially be treated with an aminosalicylate (5-ASA). Patients failing therapy with these agents will generally be treated with systemic corticosteroids, which are effective for short-term induction but not for maintenance. After one year, only about 30% of mainly prednisone-treated CD patients were in response (Faubion *et al* 2001). Approximately 40% had a relapse of

symptoms and required surgical resection and 30% became steroid-dependent. This is of particular concern due to the well-known systemic toxicities associated with long-term steroid use and their potential life-threatening complications. In addition to increasing the overall risk of infection, pre-operative treatment with steroids has been shown to increase the risk of post-operative complications and sepsis (Aberra *et al* 2003).

A patient who fails treatment with oral steroids, either by lack of response, steroid intolerance, or by repeated disease flares while attempting to reduce the dose of the drug, may then be given an immunosuppressant (e.g., azathioprine, its metabolite 6-mercaptopurine, or methotrexate). Immunosuppressants are unapproved therapies with modest efficacy. However, rare, serious side-effects can occur with the use of azathioprine/6-mercaptopurine such as bone-marrow suppression, hepatotoxicity, pancreatitis, and serious infectious, including systemic viral infections (e.g., cytomegalovirus and varicella zoster) (Siegel and Sands 2005; Travis 2006). At the moment, the relationship between the use of thiopurines and the risk of lymphoma development is unclear. The major toxic effects of methotrexate are generally similar to those of azathioprine and also require careful monitoring.

The TNF α inhibitors, infliximab and adalimumab, are approved for use in patients with an inadequate response to the above conventional therapy.

1.3 THE UNMET MEDICAL NEED IN CD

The major unmet need is for a therapy that can be used in patients who have failed the above therapies. Two TNF-α inhibitor therapies, infliximab and adalimumab, are approved to treat patients with moderately to severely active CD who have had an inadequate response to conventional therapy. More than 40% of CD patients are non-responders to their initial TNF-α inhibitor therapy (Hanauer 2002; Hanauer 2006; Humira Prescribing Information). Furthermore, approximately 40% of those that do initially respond to the TNF-α inhibitor therapy will maintain clinical response after a year of treatment and less than 30% of initial responders will remain in remission at one year without the use of corticosteroids (Remicade Prescribing Information). A need for new therapies that maintain clinical response and remission in patients with active CD exists.

Consistent with their mechanism of action, there are recognized safety concerns associated with increased morbidity or mortality with anti-TNF therapies. These risks include OI's (particularly tuberculosis and histoplasmosis) and malignancies (primarily lymphoma). Other events that have been attributed to treatment with TNF-α inhibitor therapy include a lupus-like syndrome and autoimmunity, neurological disorders including demyelination, hepatoxicity, and worsening of congestive heart failure. Mortality possibly attributable to infliximab use was estimated to be as high as 1-2% in referral centers as well as in epidemiologically well-defined patient cohorts (Colombel 2004; Ljung 2004; Lichtenstein 2006). Recent reports of hepatosplenic T-cell lymphoma in CD patients receiving infliximab, in combination with azathioprine or

6-mercaptopurine, highlights the potential risk of this combined therapy (Remicade Prescribing Information, 2006).

In those who fail TNF-α inhibitor therapy, current options include surgery or experimental therapies with unproven efficacy and unknown safety. Surgery is used to treat complications such as bowel obstruction or abscess or to control the patient's symptoms when medical therapy fails, though surgical intervention is not curative for CD. Further, there is a high post-operative recurrence rate with most patients having at least endoscopic evidence of recurrent disease within a year of surgery.

It is anticipated that the availability of natalizumab, with its novel mechanism of action, will offer patients and physicians additional treatment options, particularly for patients who have failed conventional therapy.

1.4 NATALIZUMAB AND α-INTEGRINS

Natalizumab is a recombinant humanized anti-α4 integrin monoclonal antibody that is produced in NS0 murine myeloma cells and binds to the α4 subunit of human integrin, expressed at high levels on all circulating leukocytes, except neutrophils, and on haematopoietic progenitor cells. Integrins are glycoproteins composed of two noncovalently linked α and β subcomponents. They are a class of adhesion molecules that mediate the attachment of leukocytes to vascular endothelial cells lining blood vessels and facilitate their migration into the tissue. Through interactions with extracellular matrix molecules, adhesion molecules then support immune cell activation and survival.

Natalizumab binds to α4β1 integrin (also known as very late antigen 4 [VLA-4]) and blocks the interaction with its counter-receptor on endothelial cells, VCAM-1. VCAM-1, which is not normally expressed on gut endothelial cells, is upregulated in response to inflammatory cytokines in the setting of CD (Briskin *et al* 1997). Similarly, natalizumab blocks the interaction of α4β7 integrin (which is also expressed on leukocytes) with MAdCAM-1, another counter-receptor. MadCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to gut lymph tissue found in Peyer's patches. Disruption of these molecular interactions prevents trafficking of mononuclear leukocytes across the endothelium and into the parenchymal tissue. Increased leukocyte trafficking into the parenchyma of the brain and gut is believed to play a role in the pathogenesis of MS and IBD, respectively.

Therefore, by disrupting the VCAM-1/α4β1 and MadCAM-1/α4β7 interactions, treatment with natalizumab is expected to reduce lymphocyte migration from the blood vessel to the area of inflammation, decrease tissue inflammation and thereby reduce the levels of cytokines and other mediators of inflammation at the site of tissue injury.

The α4 integrins bind additional ligands in tissues, including osteopontin and epitopes of fibronectin. This interaction plays a key role in supporting immune cell activation and

survival. Thus, an additional action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4 integrin-expressing leukocytes with these ligands. As such, natalizumab may act to suppress the existing inflammatory activity present within the GI tract, along with the inhibition of further recruitment of immune cells into inflamed tissue (Sandborn and Yednock 2003; von Andrian and Engelhardt 2003 in Module 5.4).

1.5 PATIENT POPULATION

Natalizumab demonstrated anti-inflammatory activity in preclinical models of inflammatory bowel disease and was thus developed as a treatment for patients with active CD. It was predicted that the putative mechanism of action of natalizumab would interrupt the ongoing inflammatory process in CD and provide clinical benefit. The Phase 3 program was designed to assess efficacy and safety in patients with moderately to severely active CD. Results from both induction studies indicate that initial assessments of CRP, as an objective marker of inflammation, will have utility in reducing the proportion of patients who may have a spontaneous response.

Natalizumab is thus targeted as a potential therapy for patients with moderate to severe, active CD in whom objective evidence of inflammation (as defined by elevated CRP or other objective marker) is present. The drug is recommended for use only in patients who have failed therapy with conventional agents (steroids and immunosuppressant drugs). However, due to potential safety concerns, natalizumab is likely to be used initially in those patients who have also failed an inhibitor of TNF-α. Data will be presented demonstrating efficacy on a broad range of outcomes and in relevant subgroups.

1.6 CLINICAL DEVELOPMENT PROGRAM FOR NATALIZUMAB

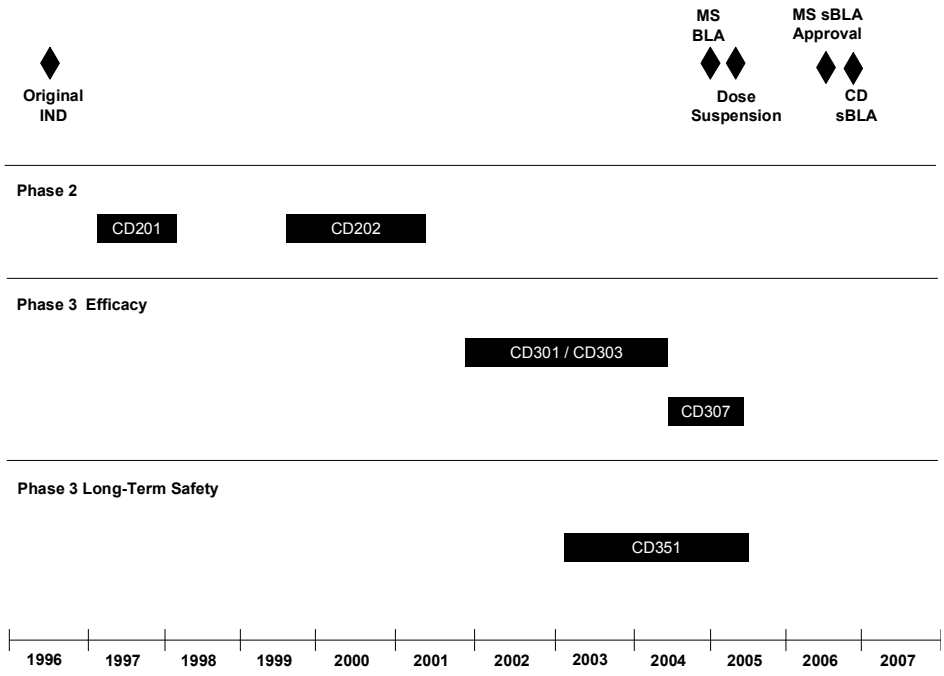
Natalizumab has been studied as a treatment for CD, MS, and rheumatoid arthritis (RA) for approximately 10 years (Figure 1), although the development program in RA has been discontinued. Elan and Biogen Idec have conducted the development of natalizumab for CD in North America, Europe and other selected countries. Eleven Phase II/III clinical studies in patients with CD have been completed, including three Phase III efficacy studies: ELN100226-CD307 (CD307)[2], AN100226-CD301 (CD301) and AN100226-CD303 (CD303) (Figure 1). The remaining CD studies are summarized below.

Clinical development in CD began with single-dose healthy volunteer studies followed by a single-dose, pilot Phase 2 study, CD201, and a large multi-dose Phase 2 study, CD202. These initial studies and those in MS used weight-based dosing and determined that doses in the 3 to 6 mg/kg range were effective with similar efficacy and safety. Based upon pharmacokinetic (PK) and pharmacodynamic (PD) data from these studies, a fixed dose of 300 mg was chosen as a dose likely to achieve an adequate level of α4-integrin receptor saturation throughout the dosing interval across a broad patient

[2] For brevity, the prefix 'AN100226-' or 'ELN100226-' is omitted from all study numbers

spectrum. The efficacy of 300 mg natalizumab administered every 4 weeks as an IV infusion over 1 hour was compared to placebo in the two CD Phase 3 induction trials, Studies CD301 and CD307. After completing their participation in Studies CD301, responders could be re-randomized to receive placebo or 300 mg natalizumab every 4 weeks in a 12-month study to evaluate the ability of natalizumab to sustain a treatment response (CD303).

Figure 1 Clinical Development Program of Natalizumab in CD



Details of the Phase III efficacy studies are provided in Section 2.

Supportive Studies: Eight supportive studies (CD201 and CD202, CD251 and CD305, CD306, CD351, CD352, and CD354) have been undertaken with natalizumab in patients with CD. Efficacy results for placebo-controlled Phase II study CD202 (one or two doses of study drug, using a weight-based regimen) were used to help select the 300 mg dose for evaluation in the pivotal studies. The remaining studies were primarily safety studies, open-label studies or studies in a population other than the proposed indicated patient population. These studies were a pilot study CD201 (Gordon *et al* 2001), a 2-year open-label extension study (CD351) and its follow-on study (CD354), an intermittent natalizumab re-treatment study (CD251), a study of natalizumab in combination with infliximab (CD306), and an open-label study in adolescent patients (CD305) and its extension (CD352).

2 OVERVIEW OF EFFICACY

Efficacy of natalizumab has been demonstrated in 3 randomized placebo controlled Phase III studies: CD307, CD301 and CD303. These studies were conducted worldwide, with most centers in the US and Europe. Studies were randomized, double-blind, placebo-controlled, parallel-group designs (Table 4).

Both studies CD307 and CD301 evaluated the ability of natalizumab to induce a clinical response and were of similar design. In study CD307, 509 patients with moderately to severely active CD, and who had an elevated CRP, were randomized to receive 3 infusions of natalizumab, or placebo, using a 1:1 allocation. In study CD301, 905 patients with moderately to severely active CD were randomized to natalizumab or placebo using a 4:1 allocation. In study CD303, patients who responded in study CD301, were re-randomized to natalizumab or placebo, using a 1:1 allocation, and maintenance of response was evaluated over a 12-month period. Further long-term efficacy and safety data were obtained in a large open-label extension study, CD351.

Efficacy parameters assessed in CD307 and CD301 included the proportion of patients who achieved clinical response and clinical remission (as determined by CDAI score), effects on objective markers of inflammation (such as CRP), and effects on HRQoL using the IBDQ and SF-36 instruments. CD303 assessed the proportion of patients who sustained response and remission following induction therapy, the proportion of patients who achieved steroid elimination, and effects on HRQoL.

CD307 demonstrated that natalizumab is efficacious for the induction of response and remission in patients with moderately to severely active CD, and who have an objective marker of inflammation such as elevated CRP, while CD301 provided strong supportive evidence for these findings. Maintenance of response and remission over 12 months was demonstrated in CD303, as were reduction of steroid use and near-normalization of HRQoL.

Taking into account concerns regarding the effect of immunosuppression on the occurrence of PML and other serious OI's, the Sponsor has performed post-hoc, safety-driven analyses of the clinical data. The efficacy of natalizumab treatment without the use of a concomitant immunosuppressant (such as azathioprine) is shown in Section 2.2.7.

Table 4 Summary of Natalizumab Phase III Efficacy Studies

Study Dates	Design	Treatment Groups	No. Patients Enrolled
Induction (Primary)			
CD307 2004-2005	1:1 randomization Visits at 4-week intervals	Three IV infusions separated by 4 weeks Placebo Natalizumab 300 mg	 250 260[a]
CD301 2001-2003	1:4 randomization Visits at 2-week intervals	Three IV infusions, separated by 4 weeks Placebo Natalizumab 300 mg	 181 724[a]
Maintenance (Primary)			
CD303 2001-2003	Responders in CD301 re-randomized at entry to CD303 1:1 randomization Visits at 4-week intervals	Twelve IV infusions, separated by 4 weeks Placebo Natalizumab 300 mg	 171 168

[a] One of 260 patients in CD307 received natalizumab but was not randomized and was excluded from the ITT Population. One of 724 patients in CD301 was randomized to receive natalizumab but did not receive study drug, this subject was included in the natalizumab group for the ITT Population.

2.1 PATIENT POPULATIONS STUDIED

Patients with moderately to severely active CD, as defined by a CDAI score of 220 to 450, were studied in two Phase III induction studies (CD307 and CD301). In CD307 patients were required to have an elevated CRP (>ULN) at screening (see Section 1.1.3).

Patients in CD307 and CD301 were allowed to receive concomitant medication for CD such as 5-aminosalicylate (5-ASA) compounds, steroids, and/or immunosuppressants (e.g. azathioprine, 6-mercaptopurine or methotrexate) as long as they had been on a stable dose for a defined period (stated in the protocol). Concomitant use of an anti-TNF therapy, such as infliximab, was not permitted in either study or in the maintenance study CD303.

Patients who responded to treatment in the induction study CD301 were re-randomized to receive natalizumab or placebo, every month, for 12 months in study CD303. To enter CD303, patients were required to either have mildly active CD (CDAI score of ≥150 and <220) with a ≥70 points reduction in their CDAI score from CD301 baseline level or to be in remission (CDAI score <150). Patients were allowed to discontinue steroids in accordance with a fixed algorithm set out in the CD303 protocol.

Baseline demographic data for the populations across studies CD307 and CD301 were balanced between treatment groups and generally comparable between studies. Mean CDAI scores across treatment groups were approximately 300, duration of CD was 9–10 years, and the mean age of patients was 38–39 years. Slightly more females than males were enrolled in both studies (57–60%). Overall median baseline CRP values were higher in CD307 than CD301 (13.7 vs 9.0 mg/L), as expected, based on a requirement for all patients enrolled in CD307 to have elevated CRP in contrast to no such requirement in CD301. Demographic and baseline characteristics for CD303 were generally balanced between the natalizumab and placebo groups.

2.2 EFFICACY RESULTS FROM THE PHASE 3 STUDIES

The Phase III induction studies CD307 and CD301 were designed to determine the proportion of patients who achieved a clinical response or remission with natalizumab, during a 3-month induction period. Clinical response was determined by a reduction of ≥70 points from baseline CDAI score. A ≥70-point reduction in score is widely accepted as being clinically meaningful, and has historically been used to determine response. Clinical remission (CDAI score <150) was pre-specified as a contingent primary endpoint in CD301 and a secondary endpoint in CD307. This section presents clinical data showing the efficacy of natalizumab to induce clinical response or remission following 3 infusions of natalizumab every 4 weeks. Data is presented for the overall (ITT) Population of CD301 and CD307, and also for a subset of patients in CD301 with elevated CRP at baseline.

The Phase III maintenance study (CD303) evaluated the proportion of patients who maintained response following 12 months of additional therapy. The primary endpoint evaluated the proportion of patients who maintained response through 6 months of therapy. The corresponding evaluation of remission was a contingent primary endpoint.

2.2.1 CD301 Induction Study

Patients with moderately to severely active CD (CDAI score of 220 to 450) were randomized (using a 4:1 allocation) to receive 3 infusions of natalizumab or placebo every 4 weeks based on baseline CDAI score and concomitant use of oral steroids. Patients were infused at Week 0, Week 4 and Week 8 and were evaluated every 2 weeks through Week 12. This randomization scheme was chosen to aid recruitment and to provide a sufficient number of natalizumab-treated responders for analysis in the maintenance study, CD303. Randomization was stratified based on baseline CDAI score and concomitant use of oral steroids. The primary endpoint was comparison, using logistic regression, between treatment groups of the proportion of patients in response (≥70-point decrease in CDAI score from baseline) at Week 10. For the primary endpoint, a non-responder was defined as a subject with <70-point decrease in CDAI score or a subject with a missing score at Week 10 or a subject who had used rescue therapy at or before Week 10. For secondary endpoints, last observation carried forward (LOCF) methodology was used to replace missing CDAI scores and all CDAI scores collected

after rescue intervention. The treatment comparison of remission (CDAI score <150) at Week 10 was a contingent primary endpoint and became a secondary endpoint if statistical significance at the 0.05 level was not achieved for the primary endpoint. This hierarchical approach protects against inflation of the probability of Type I error. The pre-specified secondary endpoints were remission at Week 4, response at Week 2, the proportion of patients at Week 10 with a ≥100-point decrease in CDAI score from baseline, and the mean change from baseline in IBDQ at Week 10. Other key endpoints included change from baseline in CDAI score and CRP levels. All these endpoints were prospectively defined.

Although not statistically significant, a higher proportion of natalizumab-treated patients than placebo patients at Week 10 experienced a clinical response (56% *vs* 49%, p=0.051;Table 5) or remission (37% *vs* 30%, p=0.124; Table 6).

Table 5 CD301: Proportion of Patients with a ClinicalResponse (ITT Population)

Visit	Placebo (n=181) N (%)	Natalizumab (n=724) N (%)	Odds Ratio (a)	95% CI of Odds Ratio (a)	p-value (a)
Week 2*	59 (33)	287 (40)	1.4	(1.0, 2.0)	0.060
Week 4	81 (45)	371 (51)	1.3	(1.0, 1.8)	0.094
Week 6	95 (52)	423 (58)	1.3	(0.9, 1.8)	0.130
Week 8	91 (50)	410 (57)	1.3	(0.9, 1.8)	0.101
Week 10	88 (49)	408 (56)	1.4	(1.0, 1.9)	0.051
Week 12	**92 (51)**	**444 (61)**	**1.6**	**(1.1, 2.2)**	**0.009**
Any Time (b)	132 (73)	555 (77)	1.2	(0.9, 1.8)	0.259

Note: Patients with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10 (primary time-point [shaded row]).

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process (disease severity [CDAI <330 *vs* ≥330] at baseline and baseline steroid use [yes/no]).

(b) Any time through Week 12

* Pre-specified secondary endpoint

Source data: CD301, Table 24

Table 6 CD301: Proportion of Patients in Clinical Remission (ITT Population)

Visit	Placebo (n=181) N (%)	Natalizumab (n=724) N (%)	Odds Ratio (a)	95% CI of Odds Ratio (a)	p-value (a)
Week 2	18 (10)	100 (14)	1.4	(0.8, 2.4)	0.225
Week 4*	34 (19)	163 (23)	1.2	(0.8, 1.9)	0.351
Week 6	**41 (23)**	**236 (33)**	**1.6**	**(1.1, 2.4)**	**0.014**
Week 8	51 (28)	246 (34)	1.3	(0.9, 1.9)	0.177
Week 10	55 (30)	267 (37)	1.3	(0.9, 1.9)	0.124
Week 12	**56 (31)**	**288 (40)**	**1.5**	**(1.0, 2.1)**	**0.037**
Any Time (b)	**79 (44)**	**391 (54)**	**1.5**	**(1.1, 2.1)**	**0.017**

* Pre-specified secondary endpoints
Table footnotes as for Table 5 .
Source data: CD301, Table 26

2.2.1.1 Secondary Endpoints

Response at Week 2 (Table 5) and remission at Week 4 (Table 6) are presented above. The proportion of patients with a ≥100-point decrease from baseline in CDAI score at Week 10 was higher for natalizumab-treated patients compared with placebo patients (49% *vs* 41%; p=0.046). In addition, the change from baseline CDAI score and change from baseline CRP (tertiary endpoints) showed statistically significant treatment advantages for natalizumab compared with placebo at the earliest timepoint (Week 2) and at each subsequent timepoint through to Week 12.

Change in IBDQ-measured HRQoL from baseline to Week 10, found natalizumab-treated patients to have greater increases as compared with placebo for the total IBDQ score (mean increase: 35.0 natalizumab *vs* 28.3 placebo; p=0.037).

High placebo response rates, as seen in this study, have been observed in other IBD studies (Anton and Shanahan 1998). Possible reasons include the partially subjective nature of the assessment scale, the 4:1 randomization scheme (leading to a smaller number of placebo patients and a greater expectation of receiving active drug in study participants) and high frequency of visits leading to augmentation of placebo effect.

2.2.1.2 CD301 Elevated CRP Population

Some patients presenting with CD may generate a CDAI score that does not reflect the inflammatory status and biological activity of the disease (Biancone *et al* 2003; Su *et al* 2004; Acciuffi *et al* 1996), so objective measures of inflammation, such as the level of CRP, may be useful in excluding patients who would not benefit from treatment. A post-hoc analysis of clinical response and remission was performed in patients with baseline CRP >2.87 mg/L (ULN) in CD301 ("Elevated CRP Population"). This subgroup comprised 73% of patients in the ITT population (134/181 [74%] placebo *vs* 526/724 [73%] natalizumab).

For the CD301 Elevated CRP Population, demographic and baseline characteristics were similar between treatment groups and with those for the CD301 ITT Population, with the expected exception that overall median baseline CRP was higher (15.3 mg/L) for the subgroup defined by increased CRP. In the CD301 Elevated CRP population, the same endpoints and analysis methods were employed as for the ITT population. At the Week 10 timepoint, 58% of natalizumab-treated patients achieved response at the Week 10 time-point compared with 45% of placebo-treated patients (p=0.007; Table 7) and 40% of patients in the natalizumab group achieved remission at Week 10 compared with 28% of patients in the placebo group (p=0.014; Table 8). Throughout the 12-week study, there was a statistically significantly difference in clinical response in natalizumab-treated patients (in the Elevated CRP Population) compared to placebo-treated patients (Table 7).

Table 7 CD301: Proportion of Patients with a Clinical Response (Elevated CRP Population)

Visit	Placebo (n=134) N (%)	Natalizumab (n=526) N (%)	Odds Ratio (a)	95% CI of Odds Ratio (a)	p-value (a)
Week 2	**42 (31)**	**221 (42)**	**1.6**	**(1.1, 2.4)**	**0.020**
Week 4	**59 (44)**	**289 (55)**	**1.6**	**(1.1, 2.3)**	**0.022**
Week 6	**66 (49)**	**328 (62)**	**1.7**	**(1.2, 2.5)**	**0.006**
Week 8	**63 (47)**	**314 (60)**	**1.7**	**(1.1, 2.5)**	**0.008**
Week 10	**60 (45)**	**303 (58)**	**1.7**	**(1.1, 2.5)**	**0.007**
Week 12	**64 (48)**	**330 (63)**	**1.9**	**(1.3, 2.7)**	**0.002**
Any Time (b)	**92 (69)**	**412 (78)**	**1.7**	**(1.1, 2.5)**	**0.019**

Table footnotes as for Table 5
Source data: CD301, Table 15

Table 8 CD301: Proportion of Patients in Clinical Remission (Elevated CRP Population)

Visit	Placebo (n=134) N (%)	Natalizumab (n=526) N (%)	Odds Ratio (a)	95% CI of Odds Ratio (a)	p-value (a)
Week 2	13 (10)	75 (14)	1.5	(0.8, 2.8)	0.221
Week 4	25 (19)	126 (24)	1.3	(0.8, 2.2)	0.251
Week 6	**30 (22)**	**186 (35)**	**1.9**	**(1.2, 3.0)**	**0.006**
Week 8	36 (27)	191 (36)	1.5	(1.0, 2.3)	0.054
Week 10	**37 (28)**	**208 (40)**	**1.7**	**(1.1, 2.6)**	**0.014**
Week 12	**39 (29)**	**220 (42)**	**1.7**	**(1.1, 2.6)**	**0.010**
Any Time (b)	**56 (42)**	**295 (56)**	**1.8**	**(1.2, 2.6)**	**0.005**

Table footnotes as for Table 5
Source data: CD301, Table 20

Results of this post hoc analysis indicated that an enhanced treatment effect was observed in patients with elevated baseline CRP compared with the overall CD301 ITT Population. Consequently, the second induction study, CD307, was specifically designed to test the hypothesis that natalizumab is an effective induction therapy in patients with objective evidence of active inflammation, such as elevated CRP.

In addition to the requirement for patients to enroll with elevated CRP, the following design modifications in CD307 aimed to reduce placebo response: an equal natalizumab/placebo randomization replaced the 4:1 ratio in CD301 and efficacy evaluations were to be performed every 4 weeks (instead of every 2 weeks). Finally, to ensure measurement of a more durable effect, the improvements in CDAI score leading to designation as response or remission were required to be maintained at both weeks 8 and 12, rather than just a single time-point.

2.2.2 CD307 Induction Study

Study CD307 enrolled patients with moderately to severely active CD (CDAI score 220 to 450) and elevated CRP at screening. Patients were randomized on a 1:1 basis to receive 3 infusions of natalizumab or placebo every 4 weeks (i.e. patients were infused at Week 0, 4 and 8 and evaluated though Week 12). A total of 509 patients (259 natalizumab; 250 placebo) were evaluated.

The primary endpoint measure was the proportion of patients in response (≥70-point decrease in CDAI score from baseline) at both Weeks 8 and 12, analyzed by logistic regression adjusting for disease severity at baseline (i.e. CDAI <330 or ≥330). Patients were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event. If the CDAI score was missing for a given time point, the subject was considered a treatment failure for that time point. Randomization was stratified by site. Pre-specified secondary endpoints included the proportion of patients in remission (CDAI score <150) at both Weeks 8 and 12, the proportion in response at Week 12 and the proportion in remission at Week 12.

A higher proportion of natalizumab-treated patients, than placebo patients, experienced a clinical response (48% *vs* 32%; p<0.001)(Table 9) and remission (26% *vs* 16%; p=0.002) (Table 10) at both Weeks 8 and 12. In addition, a significantly higher proportion of natalizumab-treated patients, compared with placebo, were in response and remission, the secondary endpoints, at Week 12. Importantly, a significant treatment difference between the natalizumab and placebo groups was seen at the earliest time-point (Week 4).

Table 9 CD307: Proportion of Patients with a Clinical Response (ITT Population)

Visit	Placebo (n=250) N (%)	Natalizumab (n=259) N (%)	Odds Ratio (a)	95% CI of Odds Ratio (a)	p-value (a)
Week 4	92 (37)	133 (51)	1.8	(1.3, 2.6)	0.001
Week 8	99 (40)	146 (56)	2.0	(1.4, 2.8)	<0.001
Week 12*	109 (44)	155 (60)	2.0	(1.4, 2.8)	<0.001
Weeks 4 & 8	62 (25)	109 (42)	2.2	(1.5, 3.2)	<0.001
Weeks 8 & 12	81 (32)	124 (48)	1.9	(1.3, 2.8)	<0.001
Any Time (b)	146 (58)	192 (74)	2.0	(1.4, 3.0)	<0.001

Note 1: Patients were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event. If CDAI score was missing for a given time point, the subject was considered a treatment failure for that time point. Response at Weeks 8 & 12 is the primary endpoint [shaded row].

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for disease severity (CDAI <330 *vs* ≥330) at baseline.

(b) Any time through Week 12.

* Pre-specified secondary outcome measure

Source: Antegren_CD\CD307\Programs\t_ITT_ClinResp.sas Date: 29AUG2005

Table 10 CD307: Proportion of Patients in Clinical Remission (ITT Population)

Visit	Placebo (n=250) N (%)	Natalizumab (n=259) N (%)	Odds Ratio (a)	95% CI of Odds Ratio (a)	p-value (a)
Week 4	39 (16)	62 (24)	1.8	(1.2, 2.9)	0.009
Week 8	52 (21)	83 (32)	1.9	(1.3, 2.9)	0.002
Week 12	63 (25)	97 (37)	1.9	(1.3, 2.8)	0.001
Weeks 4 & 8	22 (9)	48 (19)	2.5	(1.5, 4.4)	<0.001
Weeks 8 & 12	40 (16)	68 (26)	2.0	(1.3, 3.1)	0.002
Any Time (b)	86 (34)	121 (47)	1.8	(1.2, 2.6)	0.002

Table footnotes as for Table 9 .

Source: Antegren_CD\CD307\Programs\t_ITT_ClinRem.sas Date: 29AUG2005

Response and remission rates in the Per Protocol Population (i.e., patients with no major protocol or entry criteria violations) were consistent with the ITT Population results.

The clinical benefit of natalizumab is supported by pre-specified HRQoL analyses which were tertiary endpoints in the study. Assessments were performed at Week 0 and Week 12 in CD307. Improvements in the total IBDQ score from baseline for natalizumab-treated patients, compared with placebo, were seen at Week 12 (mean increase: 27 natalizumab *vs* 15 placebo; p<0.001) and for each of the IBDQ subscales (bowel

symptoms, systemic symptoms, social function and emotional function). Patients with an increase of 16 points are considered to have a clinically meaningful improvement in total IBDQ score (Feagan *et al* 2003; Irvine 1999). Based on this pre-defined criterion in CD307, a higher proportion of natalizumab-treated patients were IBDQ responders compared with placebo patients (53% *vs* 39%; p=0.003).

Of the two summary scales of the SF36, greater improvements in the physical component summary (PCS) score were observed with natalizumab compared with placebo (mean 5.8 *vs* 2.7; p<0.001) and there was a greater increase with natalizumab in the mental component summary (MCS) score that approached significance (mean 4.9 *vs* 2.6; p=0.052). A minimally important difference for each SF-36 scale is typically 5 points (Samsa *et al* 1999). Based on this pre-defined tertiary endpoint, a higher proportion of natalizumab-treated patients were responders at Week 12 compared with placebo patients for PCS, MCS and six of the eight components of SF-36.

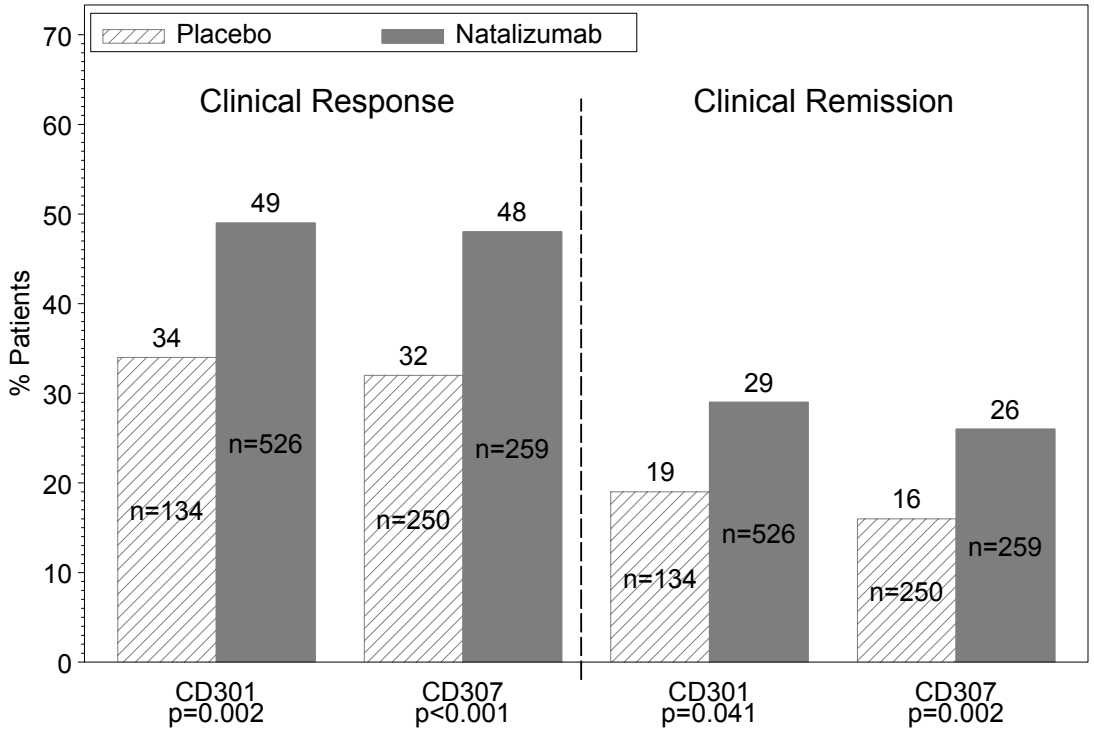
In addition to response, remission and HRQoL, a statistically significant difference between natalizumab and placebo was seen in the proportion of patients at each time-point with a ≥100-point decrease in CDAI score from baseline and mean decrease in CDAI score over time. In addition to the clinical measures, significantly greater reductions in inflammatory markers (CRP, platelet count) over time were seen with natalizumab treatment compared to placebo.

In summary, results from Study CD307 demonstrate early, consistent, and clinically relevant induction efficacy with natalizumab treatment in patients with both moderately to severely active CD and objective evidence of active inflammation, as defined by elevated CRP.

2.2.3 CD301 Elevated CRP vs CD307 ITT Populations

To facilitate comparison between the two induction studies, similar analysis algorithms were used for the CD301 Elevated CRP Population as were used for the CD307 ITT population (Figure 2):

Figure 2 Response and Remission at both Weeks 8 & 12: CD301 (Elevated CRP Population) and CD307 (ITT Population)



P-values are from logistic regression adjusting for disease severity (CDAI < 330 vs >= 330) at baseline
Source: Antegren_CD\CD_BLA\Programs\f_301_307_RemResp812_elevcrp_round.sas Generated: 03APR2007

The proportion of patients in clinical response at both Weeks 8 and 12 was higher for the natalizumab group compared with placebo for both the CD307 ITT Population and the CD301 Elevated CRP Population ($p<0.001$ and $p=0.002$, respectively) and the rates of response were consistent in both studies. Similarly, the proportion of patients in clinical remission was consistently higher for the natalizumab group compared with placebo in both the CD307 ITT Population and the CD301 Elevated CRP Population ($p=0.002$ and $p=0.041$, respectively).

In summary, the consistent effect of natalizumab has been demonstrated in patients with elevated CRP in Study CD307. Using the same analysis method, post-hoc analysis of data from the corresponding elevated CRP population in CD301 is consistent with that seen in CD307. These study results demonstrate that natalizumab is effective in inducing response and remission in patients with moderate to severe CD with objective evidence of active inflammation.

2.2.4 CD303 Maintenance Study

CD303 was a randomized maintenance study in which patients who demonstrated a clinical response after the final dose of study drug in CD301 (Week 10) and were still in response at Week12 were re-randomized to natalizumab or placebo using a 1:1 allocation. Patients and study personnel remained blinded to drug allocation in CD301 throughout study CD303. Infusions and assessments were conducted every 4 weeks for an additional 12 months (i.e., through Month 15 of CD303). Randomization was stratified according to three factors: disease status at Week 12 in CD301 (remission versus no remission), use of oral steroids at entry to Study CD301, and use of immunosuppressants at entry to Study CD301.

The primary endpoint was the proportion of patients (who responded to natalizumab in CD301) who maintained response at every visit through Month 9, analyzed by logistic regression adjusting for stratification factors. Loss of response was defined as either a CDAI score ≥220 and a ≥70-point increase from the baseline (entry to CD303) or the use of rescue intervention. Subjects who withdrew early, had 50% or more missing CDAI scores, or a missing CDAI score at a specified timepoint were also considered to have lost response. The contingent primary endpoint was the proportion of patients who maintained remission at every visit through Month 9. Loss of remission was defined as a CDAI score ≥150 or use of rescue medication. Pre-specified secondary endpoints included maintenance of response through Month 15, maintenance of remission through Month 15, time to loss of response, time to loss of remission, mean change in IBDQ from CD301 baseline to Month 9, proportion of patients not taking oral steroids at Month 9, and proportion of patients in remission and not taking oral steroids at Month 9.

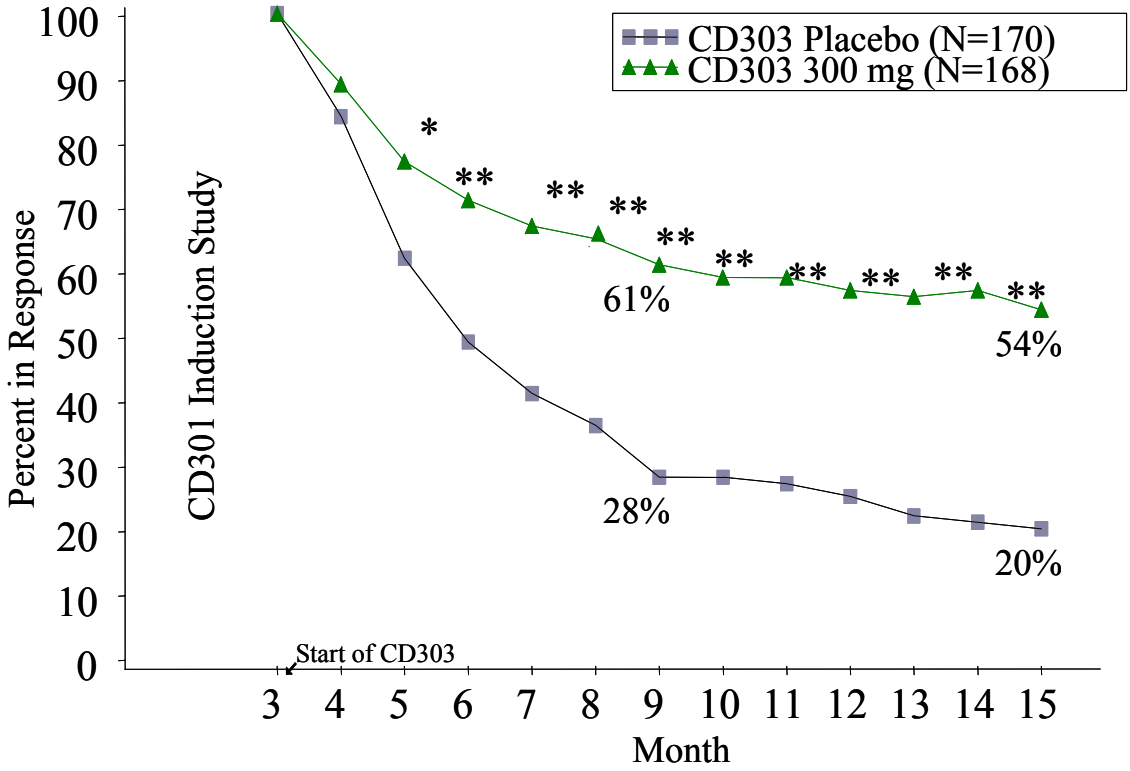
A total of 339 patients who received natalizumab in CD301 were in response at the end of CD301 and were re-randomized in CD303 (168 natalizumab, 171 placebo), the CD303 "Efficacy Population". The CD303 Remission Population was a subset of the Efficacy Population, it included patients who were in remission in CD301 and were re-randomized into CD303.

2.2.4.1 Sustained Maintenance of Response

Analysis of the primary endpoint demonstrates that more than twice the proportion of patients receiving natalizumab, compared with placebo, maintained clinical response at every visit through Month 9 (103/168 [61%] *vs* 48/170 [28%]; p<0.001) (Figure 3).

The proportion of natalizumab-treated patients who maintained response at every visit through Month 15 (secondary endpoint) was also more than twice that of placebo patients (90/168 [54%] *vs* 34/170 [20%]; p<0.001) (Figure 3).

Figure 3 CD303: Proportion of Patients with Sustained Clinical Response Over Time (Efficacy Population)



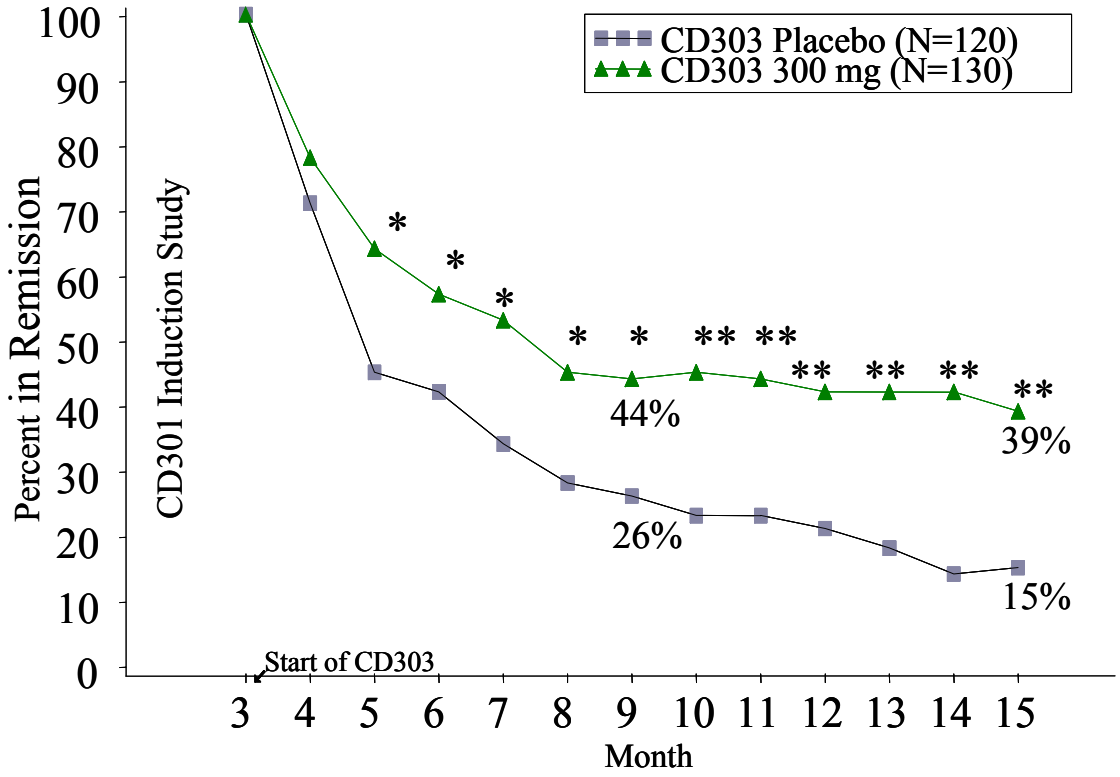
* indicates p-value<0.05 in a logistic regression adjusting for stratification factors.
** indicates p-value<0.001 in a logistic regression adjusting for stratification factors.
Source: Antegren_CD\CD_BLA\Programs\f_303_nat_PctRespTimeAnno_round.sas Date Generated: 03APR2007

Note: One placebo subject was in remission at Month 3 but not in response and is excluded from the analysis of sustained response but was included in the analysis of sustained remission.

2.2.4.2 Sustained Maintenance of Remission

CD303 included maintenance of remission as a contingent primary endpoint. The proportion of natalizumab-treated patients who maintained clinical remission at every visit through Month 9 was 44% (57/130) for natalizumab versus 26% (31/120) for placebo (p=0.003). More than twice the proportion of natalizumab-treated patients compared with placebo patients maintained remission at every visit through Month 15 (51/130 [39%] *vs* 18/120 [15%]; p<0.001) (Figure 4).

Figure 4 CD303: Proportion of Patients with Sustained Clinical Remission Over Time (Remission Population)



* indicates p-value<0.05 in a logistic regression adjusting for stratification factors.
** indicates p-value<0.001 in a logistic regression adjusting for stratification factors.
Source: Antegren_CD\CD_BLA\Programs\f_303_nat_PctRe misTimeAnno_round.sas Date Generated: 03APR2007

In addition, statistically significant treatment improvements with natalizumab compared with placebo were maintained through Month 15 for other measures of clinical outcome, including measures of active inflammation, such as CRP, platelet counts, and serum albumin levels.

2.2.4.3 Per Protocol Population

Maintenance of response and remission in patients with no major protocol or entry violations was consistent with results obtained for the respective overall populations.

2.2.4.4 Time to Loss of Clinical Response or Remission (Secondary Endpoints)

The median time to loss of response in the natalizumab group could not be determined as most patients maintained clinical response through Month 15. The median time to loss of response in the placebo group was 86 days. A comparison of the distribution of time to loss of response showed a statistically significant difference favoring the natalizumab group ($p<0.001$). The median time to loss of remission was 137 days for the natalizumab

group and 59 days for placebo. A comparison of the distribution of time to loss of remission showed a statistically significant difference favoring the natalizumab group ($p<0.001$).

2.2.4.5 Discontinuation of Oral Steroids in CD303 (Secondary Endpoints)

Study CD303 was designed to investigate the ability of patients to discontinue the use of oral steroids with natalizumab maintenance treatment. Patients followed a protocol-defined steroid withdrawal algorithm during CD303 that was initiated at Week 10 of the prior study (CD301). The protocol-mandated steroid taper in CD303 but patients whose symptoms worsened were allowed to halt the taper or increase their dose to baseline levels. Any subject increasing their dose above baseline level was considered a treatment failure. The proportion of patients not taking oral steroids at Month 9 and those in clinical remission and not taking oral steroids at Month 9 were prospectively defined as secondary endpoints, the corresponding analysis of patients in response was a post-hoc analysis.

Discontinuation of oral steroids was assessed in the CD303 Efficacy Population. The proportion of patients in response or remission who were able to discontinue their oral steroids at Months 9 (pre-specified secondary endpoint) and 15 are summarized in Table 11. Differences favoring the natalizumab group were observed at the pre-specified endpoint of Month 9 in the proportion requiring steroid use (p<0.001). The related secondary endpoint of steroid-free remission at Month 9 was also significant (p=0.014).

Table 11 CD303: Proportion of Patients who Discontinued Oral Steroids (Efficacy Population using Steroids at CD301 Baseline)

Visit	Placebo (n=76) N (%)	Natalizumab (n=67) N (%)	Odds ratio[1] (95% CI)	p-value[1]
Patients who Discontinued Steroids				
Month 9*	21 (28)	39 (58)	3.4 (1.7, 7.1)	<0.001
Month 15	15 (20)	33 (49)	3.6 (1.7, 7.7)	<0.001
Patients in Response and who Discontinued Steroids				
Month 9	19 (25)	35 (52)	3.0 (1.5, 6.3)	0.003
Month 15	13 (17)	30 (45)	3.6 (1.6, 7.8)	0.001
Patients in Remission and who Discontinued Steroids				
Month 9*	17 (22)	30 (45)	2.5 (1.2, 5.3)	0.014
Month 15	11 (14)	28 (42)	3.9 (1.7, 8.8)	0.001

* Pre-specified secondary endpoints

CI = confidence interval

[1] Adjusted odds ratio, 95% CI and p-value are from logistic regression adjusting for the stratification factors used in randomization.

Source: CD303, Table 12 and Table 13, Summary of Clinical Efficacy, Appendix 15.

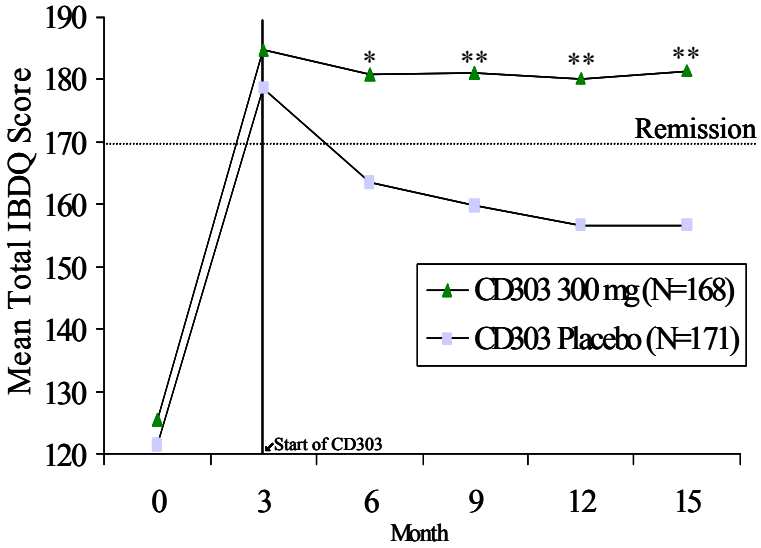
2.2.4.6 Health-Related Quality of Life (HRQoL) (Secondary Endpoints)

A HRQoL dossier was submitted to the FDA as part of the natalizumab sBLA for CD. A synopsis of key CD303 results from this dossier are provided below.

At entry into CD303, the mean total IBDQ scores were similar for patients re-randomized to natalizumab or placebo (184.9 vs 178.5). These values reflect an improvement of 59.2 and 57.0 points respectively from the CD301 baseline, and exceed 170, the lower limit of values for IBDQ seen in patients deemed “in remission”. Analysis of the secondary endpoint measure of change from CD301 baseline at Month 9, found significantly greater improvements in HRQoL with natalizumab compared to placebo, as measured by the total IBDQ scale (secondary endpoint) (bowel symptoms, systemic symptoms, emotional

function and social function). Figure 5 presents the mean total IBDQ scores of natalizumab and placebo patients both at Month 9 and also at Month 15 of CD303. Total IBDQ scores for patients receiving natalizumab were consistently greater than 170 at each time-point (range: 180.1 to 184.9), whereas patients receiving placebo had scores that decreased over time and were below the threshold for quality of life commensurate with remission at each measurement beyond Month 3.

Figure 5 CD303: Mean IBDQ Score Over Time (Efficacy Population)



*Indicates p-value<0.01 for comparison of change from CD301 baseline
**indicates p-value<0.001 for comparison of change from CD301 baseline
Sources: Antegren_CD\CD303\Programs\t_NatlBDQtime.sas
Antegren_CD\CD303\Programs\t_NatlBDQchgtime.sas

For the total SF-36 score (a tertiary endpoint), the Physical Component Summary (PCS), Mental Component Summary (MCS) and each of the individual scales of the SF-36, a significantly greater difference in change from the CD301 baseline was observed with natalizumab compared to placebo at the Month 15 visit. With natalizumab treatment, the mean increase in the PCS from CD301 baseline across the duration of the trial ranged between 12.5 and 13.4, while the mean increase in the MCS ranged between 8.3 and 10.0. The stability in the MCS and PCS scales across the duration of Study CD303 is consistent with the total IBDQ data that demonstrated sustained HRQoL improvement during natalizumab maintenance treatment.

At Month 15, the mean change from CD301 baseline in PCS was 12.6 for the natalizumab group versus 6.8 for the placebo group, while the mean change in MCS was 9.7 and 6.8, respectively ($p<0.001$ for both comparisons) (Table 12).

Table 12 CD303: Change from Baseline to Month 15 in SF-36 Scores and Individual Components (Efficacy Population)

SF-36 Components	Natalizumab (n=168) mean (SD)	Placebo (n=171) mean (SD)	p-value[1]
Physical Component Summary (PCS)	12.6 (9.4)	6.8 (9.46)	<0.001
Mental Component Summary (MCS)	9.7 (10.55)	6.8 (12.36)	<0.001
Physical functioning (PF)	18.1 (18.21)	15.2 (21.68)	0.016
Role-physical (RP)	53.4 (41.18)	22.4 (48.16)	<0.001
Bodily pain (BP)	32.1 (22.53)	17.9 (25.13)	<0.001
General health (GH)	22.6 (22.22)	11.9 (18.66)	<0.001
Vitality (V)	27.3 (25.27)	18.9 (27.16)	0.002
Social functioning (SF)	30.3 (24.25)	20.5 (28.09)	<0.001
Role-emotional (RE)	27.8 (42.35)	20.1 (48.73)	0.002
Mental health (MH)	17.2 (19.00)	10.3 (19.18)	<0.001

[1] p-value from ANCOVA adjusting for corresponding baseline value and disease severity (CDAI <330 vs. CDAI ≥330) at baseline.

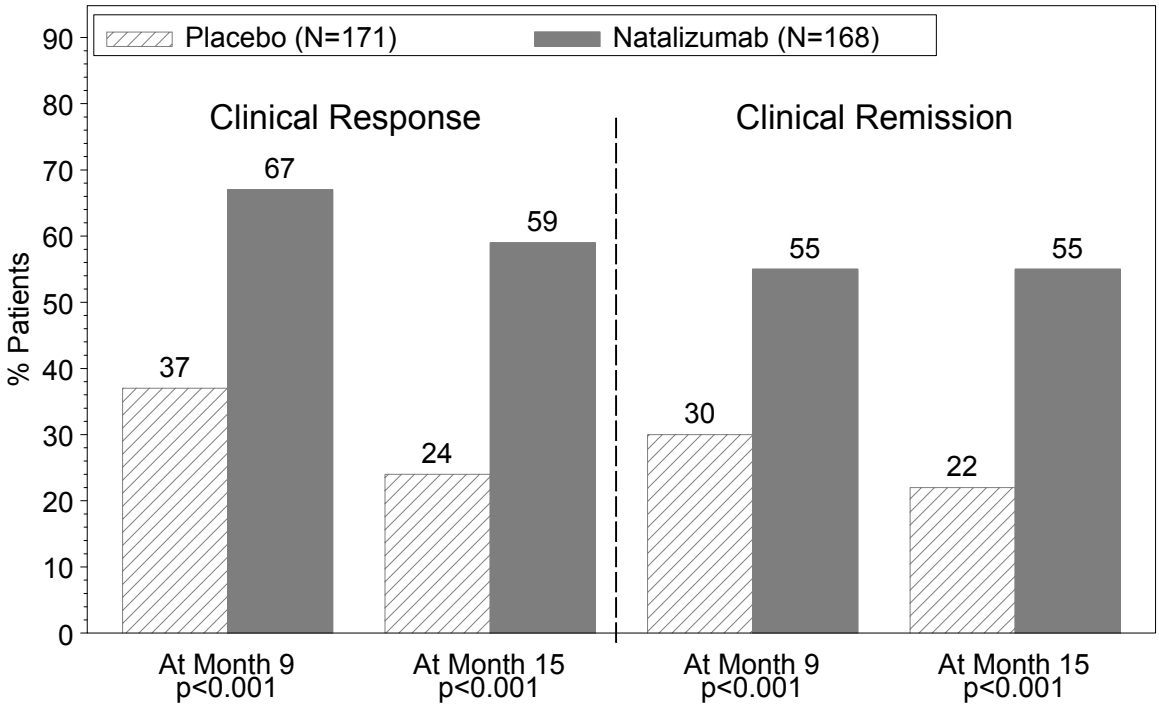
Source: CD303, Section 15.2, Table 2.12b

2.2.4.7 Point-in-Time Response and Remission

In addition to the sustained analyses presented in Section 2.2.4.2, analyses of the proportion of patients in the CD303 Efficacy Population who were in response or in remission **at** the Month 9 or Month 15 time-point (Figure 6). This was prospectively defined as a tertiary endpoint for the remission analysis and was a post-hoc analysis for response. Point-in-time analyses are commonly used to assess the efficacy of new CD therapies, including TNF-α inhibitors (Hanauer *et al* 2002).

At the Month 9 time-point, 112/168 (67%) and 93/168 (55%) patients receiving natalizumab were in response and remission, respectively, compared with 63/171 (37%) and 52/171 (30%) patients receiving placebo (p<0.001). At the Month 15 time-point, 99/168 (59%) and 93/168 (55%) patients receiving natalizumab were in response or remission compared with 41/171 (24%) and 37/171 (22%) patients receiving placebo (p<0.001).

Figure 6 CD303: Proportion of Patients in Clinical Response or Remission at the Month 9 or Month 15 Time-points (Efficacy Population)



P-values are from logistic regression adjusting for the stratification factors used in the randomization process.
Source: Antegren_CD\CD_BLA\Programs\f_303_RemResp915_Eff_round.sas Date Generated: 03APR2007

2.2.5 CD351 Long-Term, Open-Label Study

A total of 1110 patients enrolled in CD351, a long-term, open-label extension study, of whom 794 had previous natalizumab exposure in prior placebo-controlled CD studies. For patients who were in remission at entry to CD351 (n=403), 85% remained in remission following 12 months of additional therapy. A subject was considered not in clinical remission from the time of CDAI score ≥150 or time of rescue intervention onward. Although this study was open-label and lacked a control group, the results suggest a substantial and durable remission in patients who remain on natalizumab.

2.2.6 Anti-Natalizumab Antibodies and Efficacy

An ELISA screening assay was utilized to detect the presence of antibodies to natalizumab. If samples were positive in this screening assay, the serum was tested to determine if anti-natalizumab blocking antibodies were present. Since most patients who

tested positive on the screening assay were also positive with the blocking assay, this section describes results for the screening assay only.

Approximately 10% of patients were found to have anti-natalizumab antibodies at least once during study participation. Most patients (72%) had their first antibody-positive result during the first 3 months of treatment. Persistent antibodies (i.e. antibodies detected on more than one occasion) were observed in 5% of patients. In the longer-term studies CD303 and CD351, few patients (7/168 [4%] and 56/1090 [5%], respectively) had persistent antibodies, but some trends for a decrease in efficacy over time were observed in patients with persistent antibodies; no effect upon efficacy was noted with transient antibodies.

2.2.7 Efficacy With or Without Concomitant Immunosuppressants

Given the safety concern about concomitant use of biologics and immunosuppressants, it is important to determine whether efficacy of natalizumab in CD was affected by the concomitant use of immunosuppressants.

Table 13 compares the efficacy of natalizumab *vs* placebo in patients by immunosuppressant use in induction study CD307 and maintenance study CD303:

Table 13 Efficacy of Natalizumab: Effect of Concomitant Immunosuppressants

	No Immunosuppressants at Baseline[1]			Immunosuppressants at Baseline[1]		
n/N (%)	**Natalizumab**	**Placebo**	**p-value**	**Natalizumab**	**Placebo**	**p-value**
Induction (CD307) (ITT Population)[2]						
Response	81/162 (50)	49/153 (32)	0.001	43/97 (44)	32/97 (33)	0.106
Remission	41/162 (25)	25/153 (16)	0.052	27/97 (28)	15/97 (15)	0.039
Maintenance (CD303) (Efficacy Population)[3]						
Response	58/106 (55)	20/110 (18)	<0.001	32/62 (52)	14/60 (23)	0.002
Remission	32/79 (41)	12/77 (16)	<0.001	19/51 (37)	6/43 (14)	0.014

1. Patients on immunosuppressants at baseline had to have a stable dose of immunosuppressants (azathioprine, 6-MP or methotrexate) during induction and maintenance
2. Proportion of patients in response (or remission) at both Weeks 8 and 12
3. Proportion of patients in response (or remission) at Month 3 who maintained response (or remission) through 12 additional months of therapy to Month 15.

p-values are from logistic regression

Source: CD307, Tables 37 and 38; CD303, Section 15.2, Tables 2.16c and 2.17c

The majority of patients were not taking immunosuppressants on entry. For patients with no use of immunosuppressants, natalizumab-treated patients had significantly greater response rates compared to placebo patients in induction study CD307 and significantly greater response and remission rates through to Month 15 of maintenance study CD303.

The treatment difference, between active and placebo, in patients with no use of immunosuppressants was comparable to the corresponding treatment difference in patients receiving immunosuppressants.

2.2.8 Efficacy in Patients Failing Prior TNF-α Inhibitor Therapy

Natalizumab has shown efficacy compared to placebo in patients on monotherapy, as well as in those with active disease while receiving corticosteroids or immunosuppressants such as azathioprine. In addition, post-hoc analyses were conducted to evaluate the efficacy of natalizumab in TNF-α inhibitor failure patients (those who discontinued TNF-α inhibitors for lack of efficacy or intolerance).

Data is provided in Table 14 on the response and remission rates at both Weeks 8 & 12 for the prior TNF-α inhibitor failure subgroups for the CD301 Elevated CRP Population and the CD307 ITT Population. Comparative data for all patients in these populations is also provided. The overall response and remission rates were lower for the prior TNF-α inhibitor failure subgroup compared to the total population, possibly reflecting more severe disease. However, natalizumab therapy was generally effective in inducing response and remission in these patients.

Table 14 Response and Remission in Patients Failing Prior TNF-α Inhibitor Therapy

	All Patients			Failed Prior TNF-α Inhibitor Therapy		
(%) n/N	**Natalizumab**	**Placebo**	**p-value**	**Natalizumab**	**Placebo**	**p-value**
Induction (CD307) (ITT Population)[1]						
Response	48% (124/259)	32% (81/250)	<0.001	38% (34/89)	14% (12/83)	<0.001
Remission	26% (68/259)	16% (40/250)	0.002	17% (15/89)	5% (4/83)	0.012
Induction (CD301) (Elevated CRP Population)[1]						
Response	49% (260/526)	34% (46/134)	0.002	44% (60/137)	28% (11/39)	0.083
Remission	29% (151/526)	19% (26/134)	0.041	23% (32/137)	18% (7/39)	0.441

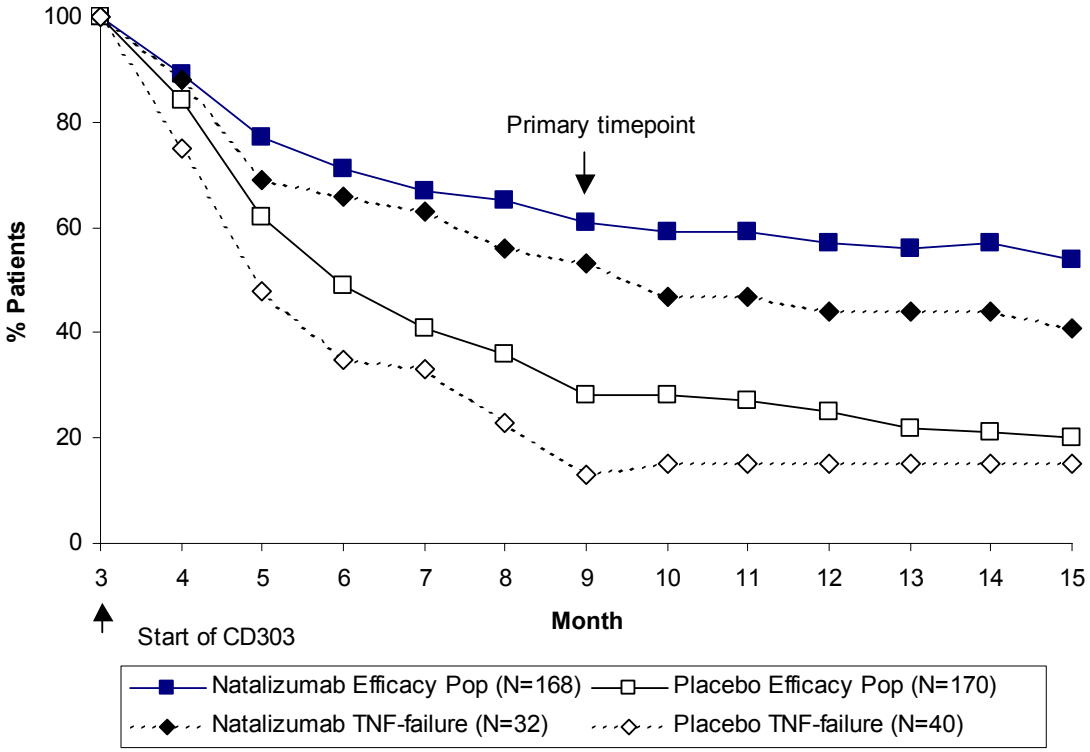
1. Proportion of patients in response (or remission) at both Weeks 8 and 12

p-values are from logistic regression adjusting for disease severity (CDAI score <330 *vs* ≥330) at baseline

Source: CD307 CSR; \CLOQ\Q1_301t__ITTClinResp[ITTClinRem]_elevcrp_nolocf.sas (04Aug2005); Antegren_CD\CLOQ_Day150\Programs\t_CD301_ITTClinResp[ITTClinRem]_antitnfFail _elevcrp_nolocf_nw (30Jan2007); CLOQ_Day150\t_307_ClinRespRem_AntiTNFFail.sas (15MAY2007)

Sustained maintenance of efficacy in the prior TNF-α inhibitor failure group was evaluated in CD303 (Figure 7) and, as for induction, response was significantly greater for patients randomized to natalizumab compared to those randomized to placebo. This finding in prior TNF-α inhibitor failures was seen through the primary timepoint of Month 9 (53% vs 13%; p<0.001) and through all other timepoints from Month 5 onwards, including the end of study timepoint, Month 15 (41% vs 15%; p=0.023).

Figure 7 CD303: Maintenance of Response in Prior TNF-α Inhibitor Failures and in the Effficacy Population



Source: CD303 CSR; CLOQ_Day150\t_303_nat_ClinRespRem_AntiTNFFail.sas (15MAY2007)

The data on induction and maintenance indicate that natalizumab is effective in patients who have continued disease activity despite having failed prior therapy with a TNF-α inhibitor.

2.2.9 Efficacy in Subgroups

In addition to the subgroups above (TNF-alpha failure subgroups, immunosuppressive use subgroup), efficacy was also analyzed based on gender, age (median age as cutoff), disease severity (CDAI above or below 330), disease duration (more than or less than 3 years), and use of steroids at baseline (yes/no) in the high CRP population of CD301, the

natalizumab responder population of CD303 and the ITT population of CD307. The point estimates of treatment effect favored the natalizumab therapy group for all subgroups. For CD301, the estimates for Odds Ratios (OR) for treatment benefit ranged from 1.2 to 2.8. Groups with lower 95%CI OR < 1 include disease duration < 3 years (0.55), CDAI >330 (0.70), steroid use at baseline (0.77), male sex (0.81), and age > 36 (0.91). For CD307, the estimates for OR of treatment effect ranged from 1.5 to 3.7 with steroid use at baseline (0.83), immunosuppressive use at baseline (0.90) and age >36 (0.97) being the only 3 of the 14 subgroups with lower 95%CI falling below 1.0. For CD303, OR estimates ranged from 2.6 to 6.0 with no group having a lower 95%CI falling below 1.0.

2.3 CONCLUSION

In summary, natalizumab has been demonstrated to be an effective induction therapy for patients with moderately to severely active CD where there is evidence of active inflammation. The onset of effect of natalizumab is generally within 4 weeks, although an additional small proportion of patients achieve response between weeks 4 and 12. Most important is the effect on maintenance of response and remission; a large proportion of patients remain in response and remission for up to 15 months with continued natalizumab treatment. Furthermore, in addition to maintaining treatment effect, therapy with natalizumab also allows for a significant proportion of natalizumab-treated patients to discontinue the use of steroids. This is an important clinical outcome due to symptom relief, improvement in quality of life, and reduction in the risk of potentially serious side effects associated with chronic corticosteroid therapy. Concomitant immunosuppressants are not required for efficacy nor needed to restrain anti-natalizumab antibody development. Natalizumab is effective in patients who have continued disease activity despite having failed prior therapy with a TNF-α inhibitor.

Importantly for patients and their families, natalizumab therapy has been shown to enhance and sustain patient HRQoL to levels approaching that of the US general population mean. The ability of natalizumab therapy to maintain disease remission, reduce the use of steroids, and significantly improve HRQoL demonstrates its value as a novel and effective therapy for the treatment of CD.

3 OVERVIEW OF CLINICAL SAFETY

This section presents an overview of the integrated safety experience with natalizumab in the clinical trial setting. The focus is on CD but, where appropriate, data from the MS experience will be provided. Safety in the CD program was analyzed in two sets of populations: the short-term placebo controlled population and the short- and long-term safety population.

The short-term placebo-controlled population comprised Studies CD201, CD202, CD301, and CD307. Studies CD301 and CD307 contributed over 80% of the total safety population. Given that the design and inclusion criteria for CD301 and CD307 were comparable and that the safety profiles were similar, the safety data for all patients has been pooled. Each study was of short duration with a maximum of three infusions. This pooling provided a dataset made up of 1,182 patients who received natalizumab (983 of whom received the fixed dose of 300mg IV every 4 weeks and the remainder, doses varying between 0.1 and 6 mg/kg) and 506 who received placebo.

The short- and long-term safety population comprises safety data from the pooled short-term placebo-controlled studies that have been integrated with data from these same patients' participation in the long-term maintenance studies (CD251, CD303, CD351) in order to ascertain the safety with continued dosing. It should be recalled that randomized patients in CD303 had received natalizumab or placebo in CD301. For patients who received placebo prior to receiving natalizumab, analyses of the short- and long-term studies only include data from the time the first dose of natalizumab was given; the placebo experience in subjects who were later treated with natalizumab was not considered. Safety data generated in the short- and long-term study population were analyzed in two ways, i.e., safety events were compared between the natalizumab and placebo treatment groups or safety events were analyzed in natalizumab-treated patients categorized by the number of natalizumab doses received without comparison to placebo. This latter analysis is of particular interest since it facilitates identification of cumulative toxicity, adverse events with delayed onset, and recurrent adverse events. In total, 1,563 CD patients received natalizumab at any time for a total exposure of 1,338 person-years of exposure (Table 15).

The safety experience in patients with MS will also be noted for events of interest, e.g. infections and malignancy, as the studies in MS provide longer-term data in a placebo-controlled setting for 2 years. The placebo-controlled experience in MS studies is based upon the pooling of data from eight placebo-controlled studies (Table 15). The pooling results in an MS population of 1,617 patients for a total of 2,668 person-years of placebo-controlled exposure to natalizumab (Table 15). Approximately two-thirds were treated for 2 years or longer. The 1,135 patients who received placebo in the eight studies form the comparison group. The patients who received either natalizumab or placebo in a placebo-controlled MS study could enrol into an open-label extension study. In total, 2,321 patients received natalizumab in MS studies contributing to a total of 3,321 person-years of exposure (Table 15).

A Phase 2, placebo-controlled study in 299 rheumatoid arthritis (RA) patients, of whom 150 received natalizumab, has completed. Thereafter, 155 patients participated in an open-label extension. The 300 mg dose was used in these trials. Deaths are the only events discussed from these studies (Table 18).

Table 15 Natalizumab Treatment: Duration and Exposure

	Multiple Sclerosis	Crohn's Disease	Total
Exposed at Any Time			
Number exposed to natalizumab	2321 (100)	1563 (100)	3884 (100)
Number exposed for 1 year or more	1180 (51)	515 (33)	1695 (44)
Number exposed for 2 years or more	1056 (45)	261 (17)	1317 (34)
Number exposed for 2.5 years or more	767 (33)	66 (4)	833 (21)
Mean exposure (years)	1.43	0.86	1.20
Overall exposure (person-years)	3321	1338	4659
Placebo-controlled Studies			
Number exposed to natalizumab	1617 (100)	1182 (100)	2799 (100)
Number exposed for 1 year or more	1117 (69)	0	1117 (40)
Number exposed for 2 years or more	1055 (65)	0	1055 (38)
Number exposed for 2.5 years or more	0	0	0
Mean exposure (years)	1.65	0.20	1.04
Overall exposure (person-years)	2668	236	2904

NOTE: Numbers in parentheses are percentages.

3.1 NON-SERIOUS ADVERSE EVENTS IN CROHN'S DISEASE CLINICAL STUDIES

Incidence of Adverse Events: Short-term Placebo-Controlled Treatment Studies of Active CD

In short-term placebo-controlled treatment studies of active CD, the incidence of common adverse events was balanced between natalizumab-treated patients and patients who received placebo: 87.4% of natalizumab-treated patients and 85.6% of placebo-treated patients reported at least one adverse event (Table 16). The most common events were headache, nausea, nasopharyngitis, abdominal pain (not otherwise specified [NOS]) and Crohn's Disease.

Five events occurred at an incidence of 2.0% or higher in natalizumab-treated patients: headache (30.8% natalizumab, 24.5% placebo), nasopharyngitis (13.4%, 9.9%), fatigue (9.1%, 7.1%), pharyngolaryngeal pain (6.3%, 4.2%) and influenza-like illness (5.9%, 3.8%).

Table 16 Short-Term Placebo-Controlled Studies of Active CD: Incidence of AEs Experienced by ≥ 5% Of Patients Receiving Natalizumab

	Placebo	Natalizumab
Number of Patients Dosed	506 (100)	1182 (100)
Number of Patients with an Event	433 (85.6)	1033 (87.4)
Event		
Headache	124 (24.5)	364 (30.8)
Nausea	76 (15.0)	192 (16.2)
Nasopharyngitis	50 (9.9)	158 (13.4)
Abdominal pain NOS	61 (12.1)	145 (12.3)
Crohn's disease	82 (16.2)	132 (11.2)
Fatigue	36 (7.1)	108 (9.1)
Arthralgia	40 (7.9)	106 (9.0)
Vomiting NOS	46 (9.1)	95 (8.0)
Dizziness	33 (6.5)	91 (7.7)
Pyrexia	28 (5.5)	80 (6.8)
Back pain	35 (6.9)	78 (6.6)
Pharyngolaryngeal pain	21 (4.2)	74 (6.3)
Influenza like illness	19 (3.8)	70 (5.9)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.

SOURCE: TYSABRICD/SU3_CD/CSR/CP-AEXPCT.SAS DATE: 21MAR2006

Incidence of Adverse Events: Short- and Long-Term Dosing in CD

The most commonly occurring events in the short- and long-term dosing in CD population in the first time interval (from the start of the first infusion to the start of the seventh) were similar to those reported in short-term placebo-controlled treatment studies of active CD. The most commonly occurring events were headache, nausea, Crohn's disease, abdominal pain NOS, nasopharyngitis, arthralgia, and fatigue.

Although the frequency for some events varied over time due to decreasing number of patients at later intervals, events generally decreased in incidence over time (Table 17). However, these data must be interpreted with caution as patient number decreases over time and time-points beyond 3 months do not include randomized patients or control data.

Table 17 Short- and Long-Term Dosing in CD: Incidence of Adverse Events Experienced by at Least 5% of Patients

Subject Cohort:	Subject Who Received 1 or More Infusions	Subject Who Received 7 or More Infusions	Subject Who Received 13 or More Infusions	Subject Who Received 19 or More Infusions	Subject Who Received 25 or More Infusions	Subject Who Received 31 or More Infusions
Time Interval:	From 1st Infusion to Start of 7th Infusion	From 7th Infusion to Start of 13th Infusion	From 13th Infusion to Start of 19th Infusion	From 19th Infusion to Start of 25th Infusion	From 25th Infusion to Start of 31st Infusion	From 31st Infusion Onwards
Number of Patients Dosed	1563 (100)	681 (100)	509 (100)	427 (100)	294 (100)	81 (100)
Number of Patients with an Event	1384 (88.5)	547 (80.3)	390 (76.6)	297 (69.6)	170 (57.8)	41 (50.6)
Event						
Headache	507 (32.4)	82 (12.0)	46 (9.0)	28 (6.6)	18 (6.1)	5 (6.2)
Nausea	284 (18.2)	74 (10.9)	37 (7.3)	18 (4.2)	10 (3.4)	1 (1.2)
Crohn's disease	266 (17.0)	93 (13.7)	51 (10.0)	31 (7.3)	24 (8.2)	6 (7.4)
Abdominal pain NOS	260 (16.6)	71 (10.4)	44 (8.6)	28 (6.6)	12 (4.1)	4 (4.9)
Nasopharyngitis	244 (15.6)	90 (13.2)	68 (13.4)	40 (9.4)	16 (5.4)	2 (2.5)
Arthralgia	193 (12.3)	41 (6.0)	34 (6.7)	12 (2.8)	15 (5.1)	4 (4.9)
Fatigue	174 (11.1)	27 (4.0)	23 (4.5)	10 (2.3)	3 (1.0)	2 (2.5)
Vomiting NOS	155 (9.9)	43 (6.3)	22 (4.3)	14 (3.3)	7 (2.4)	2 (2.5)
Dizziness	142 (9.1)	28 (4.1)	12 (2.4)	12 (2.8)	4 (1.4)	0
Pyrexia	131 (8.4)	18 (2.6)	14 (2.8)	6 (1.4)	6 (2.0)	2 (2.5)
Back pain	129 (8.3)	29 (4.3)	16 (3.1)	13 (3.0)	6 (2.0)	2 (2.5)
Pharyngolaryngeal pain	112 (7.2)	21 (3.1)	19 (3.7)	13 (3.0)	5 (1.7)	1 (1.2)
Influenza like illness	109 (7.0)	28 (4.1)	17 (3.3)	11 (2.6)	5 (1.7)	3 (3.7)
Influenza	90 (5.8)	36 (5.3)	20 (3.9)	12 (2.8)	8 (2.7)	3 (3.7)
Diarrhoea NOS	87 (5.6)	35 (5.1)	29 (5.7)	24 (5.6)	12 (4.1)	5 (6.2)
Upper respiratory tract infection NOS	84 (5.4)	20 (2.9)	18 (3.5)	26 (6.1)	3 (1.0)	5 (6.2)
Upper respiratory tract infection viral NOS	34 (2.2)	38 (5.6)	14 (2.8)	7 (1.6)	1 (0.3)	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term under each time interval.
3: Preferred terms are presented by decreasing incidence in the first column.
SOURCE: TYSABRICD/SU3_CD/CSR/LT-AEXPCT.SAS DATE: 23MAR2006

3.2 DEATHS IN THE CLINICAL PROGRAM

There were 18 treatment-emergent deaths in the entire natalizumab program (Table 18). In the CD program there were a total of 6 deaths (2 natalizumab patients in the short-term placebo-controlled treatment studies of active CD, 3 natalizumab patients in open label extension studies and one subject who died two months after his 22nd infusion of natalizumab). When considering the numbers of deaths, it is important to note that for CD, the exposure to natalizumab was approximately 3-fold greater than exposure to placebo. In the placebo-controlled MS experience, there were 5 deaths (2 patients had received natalizumab and 3 had received placebo) and an additional 4 deaths within the open-label experience (all patients on natalizumab). Lastly, there were 3 deaths in the RA studies (2 natalizumab patients and 1 placebo patient).

In the MS studies, apart from PML, no other safety signal was apparent from the study deaths. In the CD studies, one patient died from PML. Two additional deaths in CD were associated with opportunistic infections - bronchopulmonary aspergillosis and pneumocystis carinii pneumonia. These patients had significant co-morbidities, which may have contributed to the development of these infections (for further discussion, see Section 3.7.3.2).

Table 18 Deaths in the Clinical Program

CD Studies

Patient Number (age/sex)	Number of Infusions	Study	Cause of Death
Natalizumab			
CD009005 (75/M)	10	CD351	Pulmonary aspergillosis
CD015004 (60/M)	8	CD351	PML
CD024202 (67/M)	28	CD351	Acute myocardial infarction, left ventricular rupture, hemopericardium, cardiac tamponade, cardiogenic shock
CD072001 (42/M)	1	CD301	CO_2 asphyxiation
CD090004 (49/F)	3	CD301	Acute renal failure
CD563003 (69/M)	34	CD351	Pneumocystis carinii pneumonia

MS Studies

Patient Number (age/sex)	Number of Infusions	Study	Cause of Death
Natalizumab			
401005 (49/F)	25	1801	Alcohol intoxication
620011 (38/M)	5	1801	Metastatic malignant melanoma
176101 (5/F)	10	1804	Respiratory distress
142101 (46/F)	37 (with AVONEX)	1808	PML
131002 (27/M)	31	1808	Suicide
158104 (51/F)	31	1808	Seizure due to MS, arrhythmia
Placebo			
154114 (47/F)	6 (with AVONEX)	1802	Cardiac arrest
169102 (23/F)	18 (with AVONEX)	1802	Respiratory arrest
11499 (66/F)	4	MS231	Pleural carcinomatosis/seizure

RA Studies

Patient Number (age/sex)	Number of Infusions	Study	Cause of Death
Natalizumab			
323001 (53/F)	3	RA201	Hemoptysis, respiratory failure (due to procedural complication)
312001 (59/F)	1	RA251	End-stage rheumatoid pulmonary disease
Placebo			
360023 (67/M)	5	RA201	Circulatory and respiratory insufficiency

3.3 SERIOUS ADVERSE EVENTS IN CROHN'S DISEASE CLINICAL STUDIES

Incidence of Adverse Events: Short-term Placebo-Controlled Treatment Studies of Active CD

In the short-term placebo-controlled studies of CD, 14.9% of natalizumab-treated patients and 14.0% of those who received placebo experienced at least one serious adverse event. The most common SAEs (by System Organ Class, SOC) (Table 19) were gastrointestinal in nature (9.8% natalizumab, 9.9% placebo), the most common being Crohn's disease (5.9%, 8.7%). Serious infections and infestations were seen in 2.4% of both natalizumab-treated patients and those who received placebo, the most common being perianal abscess (0.6% in both natalizumab and placebo-treated patients) (Table 20). All other SAEs occurred at an incidence less than 1.0%, and many events were experienced by only one subject.

Table 19 Placebo-Controlled Treatment Studies of Active CD: Incidence of SAEs Summarized by System Organ Class

	Placebo	Natalizumab
Number of Subjects Dosed	506 (100)	1182 (100)
Number of Subjects with a Serious Event	71 (14.0)	176 (14.9)
Gastrointestinal disorders	50 (9.9)	116 (9.8)
Infections and infestations	12 (2.4)	28 (2.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	8 (0.7)
Musculoskeletal and connective tissue disorders	3 (0.6)	7 (0.6)
Nervous system disorders	1 (0.2)	6 (0.5)
Blood and lymphatic system disorders	0	5 (0.4)
Cardiac disorders	0	5 (0.4)
General disorders and administration site conditions	3 (0.6)	5 (0.4)
Hepatobiliary disorders	0	5 (0.4)
Immune system disorders	1 (0.2)	5 (0.4)
Pregnancy, puerperium and perinatal conditions	3 (0.6)	5 (0.4)
Renal and urinary disorders	1 (0.2)	4 (0.3)
Reproductive system and breast disorders	0	4 (0.3)
Investigations	1 (0.2)	3 (0.3)
Metabolism and nutrition disorders	3 (0.6)	3 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	3 (0.3)
Vascular disorders	4 (0.8)	3 (0.3)
Injury, poisoning and procedural complications	1 (0.2)	2 (0.2)
Psychiatric disorders	4 (0.8)	2 (0.2)
Surgical and medical procedures	0	2 (0.2)
Congenital, familial and genetic disorders	0	1 (<0.1)
Eye disorders	0	1 (<0.1)
Skin and subcutaneous tissue disorders	0	1 (<0.1)

NOTE 1: Numbers in parentheses are percentages
2: A subject was counted only once within each system organ class
3: System organ classes are presented by decreasing incidence in the Natalizumab column.

SOURCE: ANTEGREN_CD\CD_BLA\PROGRAMS\T_CP_SAESOC.SAS DATE: 15JUN2007

Table 20 Placebo-Controlled Treatment Studies of Active CD: Incidence of SAEs Occurring in >1 Subject in Natalizumab Group

	Placebo	Natalizumab
Number of Subjects Dosed	506 (100)	1182 (100)
Number of Subjects with a Serious Event	71 (14.0)	176 (14.9)
Crohn's disease	44 (8.7)	70 (5.9)
Small intestinal obstruction NOS	2 (0.4)	9 (0.8)
Abdominal pain NOS	2 (0.4)	8 (0.7)
Intestinal obstruction NOS	3 (0.6)	8 (0.7)
Perianal abscess	3 (0.6)	7 (0.6)
Intestinal stenosis NOS	0	6 (0.5)
Anaemia NOS	0	4 (0.3)
Cholelithiasis	0	4 (0.3)
Pregnancy NOS	2 (0.4)	4 (0.3)
Pyrexia	2 (0.4)	4 (0.3)
Vomiting NOS	0	4 (0.3)
Abdominal abscess NOS	1 (0.2)	3 (0.3)
Abdominal adhesions	0	3 (0.3)
Arthralgia	0	3 (0.3)
Hypersensitivity NOS	0	3 (0.3)
Intestinal fistula	0	3 (0.3)
Anal fistula	1 (0.2)	2 (0.2)
Depression	3 (0.6)	2 (0.2)
Gastroenteritis NOS	1 (0.2)	2 (0.2)
Gastrointestinal haemorrhage NOS	0	2 (0.2)
Lung adenocarcinoma NOS	0	2 (0.2)
Meningitis viral NOS	0	2 (0.2)
Nausea	0	2 (0.2)
Peritonitis	0	2 (0.2)
Pulmonary embolism	0	2 (0.2)
Small intestinal perforation NOS	0	2 (0.2)
Urinary tract infection NOS	0	2 (0.2)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.

SOURCE: ANTEGREN_CD\CD_BLA\PROGRAMS\T_CP_SAEGT1.SAS DATE: 15JUN2007

Incidence of Serious Adverse Events: Short- and Long-Term Dosing in CD

The most common SAEs in short- and long term dosing studies in CD were gastrointestinal disorders. For patients who received natalizumab in every study in which they participated, the most common event was Crohn's disease (10.8%); in contrast 12.9% of patients who received placebo in every study in which they participated experienced this SAE. In the cohort who received placebo initially followed by natalizumab, 6.7% had serious events of CD while receiving placebo and 5.2% while receiving natalizumab.

3.4 ADVERSE EVENTS LEADING TO DISCONTINUATION OF STUDY DRUG

3.4.1 Events Leading to Discontinuation of Treatment: Short-term Placebo-Controlled Treatment Studies of Active CD

One hundred and eight of 1,182 natalizumab-treated CD patients (9.1%) compared to 57/506 placebo-treated patients (11.3%) experienced an event that led to discontinuation of study drug (Table 21). The most commonly reported event was Crohn's disease (3.7% natalizumab *vs* 7.9% placebo). Urticaria, hypersensitivity, anaphylactic reaction and type IV hypersensitivity combined led 15 natalizumab-treated patients (1.3%) to discontinue study drug compared to only 1 placebo subject with urticaria (0.2%). All other events occurred with an incidence less than 1.0%. Hypersensitivity reactions occurred most commonly during the second infusion.

Table 21 Short-term Placebo-Controlled Treatment Studies of Active CD: Incidence of Adverse Events that Led to Discontinuation of Study Drug Experienced by >1 Subject in Natalizumab Group

	Placebo	Natalizumab
Number of Patients Dosed	506 (100)	1182 (100)
Number of Patients Discontinued Treatment due to an Event	57 (11.3)	108 (9.1)
Event		
Crohn's disease	40 (7.9)	44 (3.7)
Urticaria NOS	1 (0.2)	10 (0.8)
Abdominal pain NOS	3 (0.6)	5 (0.4)
Dyspnoea	0	4 (0.3)
Flushing	0	4 (0.3)
Nausea	1 (0.2)	4 (0.3)
Pruritus	1 (0.2)	4 (0.3)
Hypersensitivity NOS	0	3 (0.3)
Infusion related reaction	0	3 (0.3)
Rigors	0	3 (0.3)
Small intestinal obstruction NOS	2 (0.4)	3 (0.3)
Tremor	0	3 (0.3)
Arthralgia	0	2 (0.2)
Cholecystitis NOS	0	2 (0.2)
Cholelithiasis	0	2 (0.2)
Dermatitis allergic	0	2 (0.2)
Intestinal obstruction NOS	0	2 (0.2)
Pregnancy NOS	2 (0.4)	2 (0.2)
Rash NOS	0	2 (0.2)
Small intestinal perforation NOS	0	2 (0.2)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.
SOURCE: ANTEGREN_CD\CD_BLA\PROGRAMS\CP-AEDIS_GT1.SAS DATE: 04MAY2007

3.4.2 Events Leading to Discontinuation of Treatment: Short- and Long-Term Dosing in CD

Similar to the placebo-controlled CD experience, exacerbation of CD was the leading cause of drug discontinuation – 80/1,041 patients (7.7%) who received natalizumab only compared to 22/163 patients (13.5%) who received placebo only. In patients who initially received placebo and subsequently received natalizumab, 39/343 patients (11.4%)

stopped drug due to recurrence of CD activity (25 while on placebo and 14 while on natalizumab). Hypersensitivity NOS led to 4 patients (0.4%) discontinuing natalizumab compared to no patients receiving placebo. Additional events that caused at least 4 patients in the natalizumab group to discontinue study drug included urticaria (natalizumab *vs* placebo: 1.4 *vs* 0.6%), abdominal pain NOS (1.0 *vs* 1.2%), small intestinal obstruction (0.9 *vs* 0.6%), dyspnoea (0.7 *vs* 0%), flushing (0.6 *vs* 0%), pruritus (0.6 *vs* 0.6%), arthralgia (0.5 *vs* 0%), chest pain (0.5 *vs* 0%), vomiting (0.4 *vs* 0%), nausea (0.5 *vs* 0.6%), infusion-related reaction (0.4 *vs* 0%), and pregnancy (0.4 *vs* 1.2%).

3.5 HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions are a known risk with administration of biologic therapeutics. These reactions can be acute or delayed, local or systemic, and can range from mild to life-threatening as with anaphylactic-type reactions. The approved label for natalizumab already warns prescribers about the risk of hypersensitivity reactions with administration of natalizumab. As defined within the protocols, patients were required to discontinue study drug following any hypersensitivity event. These events included angioedema, anaphylaxis, urticaria, biopsy-proven vasculitis, and clinical syndrome diagnostic of serum sickness.

Hypersensitivity events occurring within the 2-hour infusion reaction window were defined in the study protocols as acute hypersensitivity reactions. The incidence of acute hypersensitivity reactions was determined by analyzing the adverse events occurring within two hours of the start of the infusion.

In the short-term, 300 mg placebo controlled studies in CD (CD301 and CD307), seven natalizumab-treated patients (0.7%) were considered to have an event of hypersensitivity (coded by preferred term) compared to none in the placebo group. One additional patient had an anaphylactic reaction (0.1%) that occurred during the second natalizumab infusion. Using a broader definition of hypersensitivity (hypersensitivity NOS, anaphylactic or anaphylactoid reaction, dermatitis allergic, drug hypersensitivity, urticaria NOS, vasoconstriction, urticaria generalized and erythema multiforme) the incidence of hypersensitivity was 3.5%.

Serious infusion reactions were infrequent and occurred in 5 (0.5%) natalizumab-treated CD patients and in 1 (0.2%) who received placebo. The events in the natalizumab group included hypersensitivity (3 patients), anaphylactic reaction and urticaria. The subject in the placebo group experienced sensory loss and limb venous thrombosis.

In the short- and long-term safety population, 17 of 1,381 natalizumab-treated patients (1.2%) experienced a severe infusion reaction and 9 (0.7%) patients had a reaction categorized as serious. Most serious infusion reactions occurred at the time of infusions 2 or 3. Among the 9 cases of serious infusion reaction, 5 incidents were considered hypersensitivity reactions, all of which occurred at the time of infusions 2 or 3.

Across all CD studies, investigator-reported anaphylactic or anaphylactoid reactions (serious systemic hypersensitivity reactions) occurred in 2 natalizumab-treated CD patients (0.1%). In both cases the patients recovered rapidly following discontinuation of the infusion and appropriate treatment. There were no clinical sequelae.

In summary, the incidence of hypersensitivity in the short-term placebo controlled CD trials (CD301 and CD307) was 3.5%. Across all CD studies, the incidence of serious systemic hypersensitivity reactions was 0.1%. All patients recovered without sequelae.

3.6 MALIGNANCY

Based on the mechanism of action of natalizumab, there is a theoretical basis to consider that an increased risk of development of neoplasia could occur, particularly for malignancies associated with immunosuppression.

In the short-term, placebo-controlled CD studies, the rate of malignancy in natalizumab-treated patients was higher in the natalizumab group than placebo: 1.60 (95% exact CI: 0.64 to 3.26) malignancies per 100 person-years in the natalizumab group compared to 0.60 (95% exact CI: 0.02 to 3.32) per 100 person-years in the placebo group (Table 22). However, the number of malignancies was low (seven in the natalizumab and one in the placebo treatment groups) and the confidence intervals are wide and overlapping.

In the placebo-controlled MS experience, the rate of malignancies in the natalizumab-treated group was 0.38 (95% CI: 0.19 to 0.68) per 100 person-years compared to 0.73 (95% CI: 0.41 to 1.20) per 100 person-years in the placebo group (Table 22). This difference in malignancy rates may not reflect a true difference between the CD and MS populations because the placebo-controlled CD study duration was short (1-3 infusions), compared to the longer duration placebo-controlled studies in the MS population (up to 2 years). When the short-term, placebo-controlled CD data are combined with the placebo-controlled MS experience, the overall rate of malignancy is 0.54 per 100 person-years in the natalizumab group compared with 0.72 per 100 person-years in the placebo group.

The total number of cases of malignancy occurring in the combined CD placebo-controlled and open-label CD experience is presented in Table 23. Overall 23 cases have been reported in 22 patients. The types of malignancy seen in natalizumab-treated patients is as expected for the CD population. Of these, two malignancies (renal cell carcinoma, basal cell carcinoma) occurred in patients who had received natalizumab and infliximab in combination during the 3-month study duration. There was one case each of B-cell lymphoma and of chronic lymphocytic leukemia (CLL) reported in an open-label CD study. The patient with B-cell lymphoma had received six infusions of natalizumab and was diagnosed with lymphoma 3 months later. The subject had received 14 months of 6-mercaptopurine at the time of diagnosis of lymphoma and had prior treatment with infliximab. An increased risk of lymphoma is known to occur in CD.

The patient with CLL had received 19 infusions of natalizumab and was diagnosed with CLL 20 months after the last infusion. She had received 22 months of thioguanine therapy up to the time of diagnosis of CLL

It is important to note that several of the cases either had pre-existent abnormalities, other risk factors for malignancy, such as concomitant or prior use of immunosuppressant therapies, or had very brief time since first exposure to natalizumab and onset of malignancy. Also of note is the variability in the type of neoplasm, duration of exposure, and time since last exposure to drug. A lack of control group (most events occurred during open-label studies) impedes direct comparison of rates of malignancy with matched placebo controls.

In summary, the rate of malignancies in the placebo-controlled CD experience is higher in natalizumab-treated patients compared to placebo. No increased rate was seen in the MS placebo-controlled trials in which 2 years of placebo-controlled data in over 1600 patients was available. The rates of malignancies with natalizumab treatment for the pooled MS and CD populations are within the expected rates when compared with the existing cancer registries, such as the National Cancer Institute's Surveillance Epidemiology and End Results. It is recognized that adequate assessment of risk for malignancy requires long-term exposure. Given the potentially increased rate of malignancies in natalizumab-treated CD patients, the rate of malignancy over the long-term will be evaluated through post-marketing surveillance and the CD patient observational cohort study (Section 4.2.2).

Table 22 Placebo-controlled Studies of MS and of Treatment of Active CD: Rate of Malignancies

	Multiple Sclerosis		Crohn's Disease		MS and CD Combined	
	Placebo	**Natalizumab**	**Placebo**	**Natalizumab**	**Placebo**	**Natalizumab**
Number of patients dosed	1135	1617	506	1182	1641	2799
Total person-years	2060.36	2910.37	165.66	438.63	2226.64	3348.99
Total number of malignancies (event rate)	15 (0.73)	11 (0.38)	1 (0.60)	7 (1.60)	16 (0.72)	18 (0.54)
Basal cell carcinoma	4 (0.19)	4 (0.14)	0	0	4 (0.18)	4 (0.12)
Breast cancer NOS	3 (0.15)	3 (0.10)	0	1 (0.23)	3 (0.13)	4 (0.12)
Colon cancer NOS	0	1 (0.03)	0	1 (0.23)	0	2 (0.06)
Lung adenocarcinoma NOS	0	0	0	2 (0.46)	0	2 (0.06)
Bladder cancer NOS	0	0	0	1 (0.23)	0	1 (0.03)
Breast cancer in situ	1 (0.05)	1 (0.03)	0	0	1 (0.04)	1 (0.03)
Breast cancer invasive NOS	0	0	0	1 (0.23)	0	1 (0.03)
Cervical carcinoma stage 0	0	1 (0.03)	0	0	0	1 (0.03)
Malignant melanoma	2 (0.10)	0	0	1 (0.23)	2 (0.09)	1 (0.03)
Metastatic malignant melanoma	0	1 (0.03)	0	0	0	1 (0.03)
Breast cancer metastatic	1 (0.05)	0	0	0	1 (0.04)	0
Breast cancer stage III	1 (0.05)	0	0	0	1 (0.04)	0
Malignant pleural effusion	1 (0.05)	0	0	0	1 (0.04)	0
Secretory adenoma of pituitary	1 (0.05)	0	0	0	1 (0.04)	0
Squamous cell carcinoma of skin	1 (0.05)	0	0	0	1 (0.04)	0
Uterine cancer NOS	0	0	1 (0.60)	0	1 (0.04)	0

NOTE 1: Entries are number of events (event rate). Event rate = (total number of events/total person-years) x 100.

2: Preferred terms are presented by decreasing rate in the combined natalizumab column.

NOS: Not otherwise specified.

Table 23 Reports of Malignancy in Crohn's Disease

Type of Malignancy	ID	Diagnosis	Age	# Infusions Natalizumab	Months Since Last Infusion	Potential Confounder
Cutaneous	005001	Squamous	72	13	9	Immuno
	567010	Squamous	64	18	-	Pre-existing
	801002	Squamous	43	11	-	Immuno
	130002	Melanoma	50	2	-	Pre-existing
	513003	Basal Cell	44	6	-	
	549022	Basal Cell (2 reports)	37	3	5	Immuno
Solid Tumor	008015	Breast	55	26	-	Immuno
	541003	Breast	44	3	2	Immuno
	549026	Breast	55	1	8	Immuno
	533006	Lung	59	1	-	Abnormal pre-treatment CXR
	564003	Lung	58	3	5	Smoker, Tb, asbestos
	037007	Uterine	25	0	-	Placebo
	575005	Uterine	49	4	-	
	033305	Uterine	34	4	-	
	2415	Colon	53	1	-	
	559003	Colon*	52	2	8	Immuno
	812007	Renal	30	6	-	Immuno
	064201	Rectal*	39	2	36	
	508005	Bladder	67	3	-	
	099003	Cholangiocarcinoma*	62	20	23	
Hematologic	809704	B-cell lymphoma*	49	6	3	Immuno
	099008	CLL*	45	19	20	Immuno

Immuno = taking immunosuppressive medication at the time of onset of cancer, CLL = chronic lymphocytic leukemia, CXR = chest X-ray

Pre-existing = skin or pulmonary lesions pre-dated onset of natalizumab therapy

* = in global safety database only as the event was reported after the study closed or during the Safety Assessment visits

3.7 INFECTION

This section describes the overall rates of infection and common infections (Section 3.7.1), and infections that were classified as serious (Section 3.7.2). Opportunistic infections (Section 3.7.3.2) and the herpes family of viral infections (Section 3.7.3.1) were also fully evaluated. A comprehensive discussion on PML is provided in Section 3.7.3.3.

3.7.1 Overall Occurrence of Infection

Overall Rate and Incidence of Infections: Short-term Placebo-controlled Treatment Studies of Active CD

The incidence of infections in short-term placebo-controlled studies of CD was somewhat higher in natalizumab-treated CD patients compared to placebo-treated patients (40.4% natalizumab *vs* 36.2% placebo, respectively,Table 24) and occurred at rates of 1.67 and 1.45 infections per person-year, respectively. Only four types of infection were more common (by 1.0% or more) in natalizumab-treated patients: nasopharyngitis, viral infection NOS, urinary tract infection NOS and pharyngitis viral NOS. Very few infections resulted in permanent discontinuation of study drug: 7 natalizumab-treated patients (0.6%; herpes zoster, perianal abscess, pneumonia NOS, psoas abscess, respiratory tract infection NOS, septic shock, staphylococcal sepsis) and 5 placebo-treated patients (1.0%; cellulites, oral candidiasis, 2 rectal abscesses, sinusitis NOS) discontinued treatment due to an infection.

Overall Incidence of Infections: Short- and Long-term Dosing CD Studies

Analysis of infections in the short- and long-term dosing CD studies allowed for an assessment of the incidence of infection with continued natalizumab treatment. In the short- and long-term dosing CD studies, the incidence of infection tended to decrease with continued exposure. The most common infections (>2% in infusions 1-6) reported were nasopharyngitis, influenza, upper respiratory tract infection NOS, sinusitis NOS, viral infection NOS, gastroenteritis NOS, urinary tract infection NOS, upper respiratory tract infection viral NOS, and pharyngitis viral NOS (Table 25).

Incidence of Infections: MS Studies

The incidence of infections in placebo-controlled studies of MS was balanced between natalizumab-treated and placebo-treated patients (73.7% *vs* 73.9%, respectively) and occurred at rates of 1.54 and 1.50 infections per person-year, respectively. The overall incidence of both upper and lower respiratory tract infections was very similar in both groups (natalizumab *vs* placebo: 59.6% *vs* 59.8% upper respiratory tract; 13.3% *vs* 12.2% lower respiratory tract). Only four types of infection were more common (by 1.0% or more) in natalizumab-treated than placebo-treated patients: influenza, pharyngitis, gastroenteritis NOS, and tonsillitis. Since the longest duration of exposure to natalizumab was in patients who participated in Studies 1801 and 1802, the incidence of

infections was analyzed by 6-month intervals to determine if there was an increasing risk of infection with increasing natalizumab exposure. The risk of infection remained constant throughout the treatment period with no evidence for increasing infection risk with increasing exposure to natalizumab. Very few infections resulted in the permanent discontinuation of study drug: 11 natalizumab-treated patients (0.7%) and 5 (0.4%) placebo-treated patients discontinued treatment due to an infection.

Table 24 Short-Term Placebo-Controlled Treatment Studies of Active CD: Infections with an Incidence of 1% or More

	Placebo	Natalizumab
Number of Patients Dosed	506 (100)	1182 (100)
Number of Patients with an Infection	183 (36.2)	477 (40.4)
Event		
Nasopharyngitis	50 (9.9)	158 (13.4)
Upper respiratory tract infection NOS	19 (3.8)	50 (4.2)
Influenza	23 (4.5)	46 (3.9)
Sinusitis NOS	12 (2.4)	37 (3.1)
Viral infection NOS	8 (1.6)	34 (2.9)
Urinary tract infection NOS	7 (1.4)	31 (2.6)
Gastroenteritis NOS	10 (2.0)	26 (2.2)
Pharyngitis viral NOS	4 (0.8)	23 (1.9)
Herpes simplex	4 (0.8)	15 (1.3)
Perianal abscess	4 (0.8)	13 (1.1)
Upper respiratory tract infection viral NOS	3 (0.6)	13 (1.1)
Gastroenteritis viral NOS	7 (1.4)	10 (0.8)
Bronchitis NOS	10 (2.0)	9 (0.8)
Oral candidiasis	6 (1.2)	4 (0.3)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.

SOURCE: TYSABRICD/SU3_CD/CSR/CP-INF-4.SAS DATE: 22MAR2006

Table 25 Short- and Long-Term Dosing in CD: Infections Experienced by >1 Patients with an Incidence of 1% or More

Subject Cohort:	Subject Who Received 1 or More Infusions	Subject Who Received 7 or More Infusions	Subject Who Received 13 or More Infusions	Subject Who Received 19 or More Infusions	Subject Who Received 25 or More Infusions	Subject Who Received 31 or More Infusions
Time Interval:	From 1st Infusion to Start of 7th Infusion	From 7th Infusion to Start of 13th Infusion	From 13th Infusion to Start of 19th Infusion	From 19th Infusion to Start of 25th Infusion	From 25th Infusion to Start of 31st Infusion	From 31st Infusion Onwards
Number of Patients Dosed	1563 (100)	681 (100)	509 (100)	427 (100)	294 (100)	81 (100)
Number of Patients with an Event	764 (48.9)	327 (48.0)	214 (42.0)	163 (38.2)	85 (28.9)	21 (25.9)
Event						
Nasopharyngitis	244 (15.6)	90 (13.2)	68 (13.4)	40 (9.4)	16 (5.4)	2 (2.5)
Influenza	90 (5.8)	36 (5.3)	20 (3.9)	12 (2.8)	8 (2.7)	3 (3.7)
Upper respiratory tract infection NOS	84 (5.4)	20 (2.9)	18 (3.5)	26 (6.1)	3 (1.0)	5 (6.2)
Sinusitis NOS	65 (4.2)	24 (3.5)	24 (4.7)	16 (3.7)	12 (4.1)	1 (1.2)
Viral infection NOS	55 (3.5)	19 (2.8)	6 (1.2)	7 (1.6)	2 (0.7)	1 (1.2)
Gastroenteritis NOS	45 (2.9)	14 (2.1)	15 (2.9)	7 (1.6)	10 (3.4)	1 (1.2)
Urinary tract infection NOS	41 (2.6)	8 (1.2)	3 (0.6)	9 (2.1)	5 (1.7)	1 (1.2)
Upper respiratory	34 (2.2)	38 (5.6)	14 (2.8)	7 (1.6)	1 (0.3)	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term under each column.
3: Preferred terms are presented by decreasing incidence in the first column.

SOURCE: TYSABRICD/SU3_CD/CSR/ADHOC/LT-INFXPCT-GT1.SAS DATE: 04APR2007

Table 25 Short- and Long-Term Dosing in CD: Infections Experienced by >1 Patients with an Incidence of 1% or More (cont'd)

Subject Cohort:	Subject Who Received 1 or More Infusions	Subject Who Received 7 or More Infusions	Subject Who Received 13 or More Infusions	Subject Who Received 19 or More Infusions	Subject Who Received 25 or More Infusions	Subject Who Received 31 or More Infusions
Time Interval:	From 1st Infusion to Start of 7th Infusion	From 7th Infusion to Start of 13th Infusion	From 13th Infusion to Start of 19th Infusion	From 19th Infusion to Start of 25th Infusion	From 25th Infusion to Start of 31st Infusion	From 31st Infusion Onwards
tract infection viral NOS						
Pharyngitis viral NOS	33 (2.1)	13 (1.9)	6 (1.2)	3 (0.7)	0	0
Herpes simplex	29 (1.9)	18 (2.6)	8 (1.6)	8 (1.9)	1 (0.3)	1 (1.2)
Gastroenteritis viral NOS	25 (1.6)	10 (1.5)	13 (2.6)	5 (1.2)	5 (1.7)	2 (2.5)
Bronchitis NOS	20 (1.3)	9 (1.3)	8 (1.6)	5 (1.2)	4 (1.4)	1 (1.2)
Perianal abscess	20 (1.3)	6 (0.9)	3 (0.6)	1 (0.2)	1 (0.3)	0
Ear infection NOS	16 (1.0)	6 (0.9)	3 (0.6)	4 (0.9)	0	0
Pharyngitis	16 (1.0)	8 (1.2)	6 (1.2)	5 (1.2)	3 (1.0)	1 (1.2)
Tooth abscess	14 (0.9)	7 (1.0)	5 (1.0)	2 (0.5)	1 (0.3)	0
Tonsillitis	13 (0.8)	2 (0.3)	1 (0.2)	4 (0.9)	5 (1.7)	0
Localised infection	10 (0.6)	3 (0.4)	2 (0.4)	2 (0.5)	0	1 (1.2)
Lower respiratory tract infection NOS	9 (0.6)	4 (0.6)	9 (1.8)	3 (0.7)	5 (1.7)	0
Furuncle	8 (0.5)	1 (0.1)	6 (1.2)	1 (0.2)	2 (0.7)	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term under each column.
3: Preferred terms are presented by decreasing incidence in the first column.
SOURCE: TYSABRICD/SU3_CD/CSR/ADHOC/LT-INFXPCT-GT1.SAS DATE: 04APR2007

Table 25 Short- and Long-Term Dosing in CD: Infections Experienced by >1 Patients with an Incidence of 1% or More (cont'd)

Subject Cohort:	Subject Who Received 1 or More Infusions	Subject Who Received 7 or More Infusions	Subject Who Received 13 or More Infusions	Subject Who Received 19 or More Infusions	Subject Who Received 25 or More Infusions	Subject Who Received 31 or More Infusions
Time Interval:	From 1st Infusion to Start of 7th Infusion	From 7th Infusion to Start of 13th Infusion	From 13th Infusion to Start of 19th Infusion	From 19th Infusion to Start of 25th Infusion	From 25th Infusion to Start of 31st Infusion	From 31st Infusion Onwards
Herpes zoster	8 (0.5)	7 (1.0)	3 (0.6)	0	1 (0.3)	1 (1.2)
Upper respiratory tract infection bacterial	7 (0.4)	7 (1.0)	3 (0.6)	2 (0.5)	0	0
Folliculitis	6 (0.4)	4 (0.6)	2 (0.4)	1 (0.2)	3 (1.0)	1 (1.2)
Pneumonia NOS	6 (0.4)	6 (0.9)	7 (1.4)	1 (0.2)	2 (0.7)	0
Respiratory tract infection viral NOS	6 (0.4)	8 (1.2)	0	2 (0.5)	1 (0.3)	0
Urinary tract infection bacterial	5 (0.3)	11 (1.6)	3 (0.6)	1 (0.2)	0	1 (1.2)
Infection NOS	1 (<0.1)	0	0	0	0	1 (1.2)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term under each column.
3: Preferred terms are presented by decreasing incidence in the first column.

SOURCE: TYSABRICD/SU3_CD/CSR/ADHOC/LT-INFXPCT-GT1.SAS DATE: 04APR2007

3.7.2 Serious Infections

The incidence of serious infection in the short-term placebo-controlled studies (Table 26) was 2.5% and 2.4% in the natalizumab and placebo CD groups, respectively. The most frequently reported type of serious infection was an abscess within the gastrointestinal tract, e.g., perianal (0.6% natalizumab *vs* 0.6% placebo) and abdominal (0.3% *vs* 0.2%). Abscesses of various types occurred in <0.1% to 0.6% of patients in either treatment group. Gastroenteritis was reported with an incidence of 0.2% in each treatment group. Urinary tract infections and viral meningitis each occurred in 2 patients (0.2%) in the natalizumab group and none in the placebo group. Two placebo-treated patients (0.4%) developed sepsis and one natalizumab subject (<0.1%) developed septic shock and another developed staphylococcal sepsis. All other serious infections occurred in no more than one subject per treatment group.

In short- and long-term dosing CD studies (Table 27) the incidence of serious infection decreased with continued exposure. The most common serious infections were perianal abscess, gastroenteritis NOS, abdominal abscess NOS, bacteraemia, and gastroenteritis viral NOS.

Similar to the CD experience, the incidence of serious infection in the placebo-controlled MS studies was comparable, 2.4 % of natalizumab-treated patients *vs* 2.3% of placebo-treated patients. Appendicitis and urinary tract infection NOS were the most common serious infections (0.4% *vs* 0.3% placebo for appendicitis; 0.4% *vs* 0.2% for urinary tract infection NOS). Pneumonias, including bronchopneumonia, lobar pneumonia, and atypical pneumonia, represent 6 (0.4%) serious infections in natalizumab-treated patients and 2 (0.2%) infections in placebo-treated patients. These patients responded appropriately to antibiotic therapy.

Table 26 Short-Term Placebo-Controlled Treatment Studies of Active CD: Incidence of Serious Infections

Preferred Term	Placebo	Natalizumab
Number of Patients Dosed	506 (100)	1182 (100)
Number of Patients with a Serious Infection	12 (2.4)	29 (2.5)
Event		
Perianal abscess	3 (0.6)	7 (0.6)
Abdominal abscess NOS	1 (0.2)	3 (0.3)
Gastroenteritis NOS	1 (0.2)	2 (0.2)
Meningitis viral NOS	0	2 (0.2)
Urinary tract infection NOS	0	2 (0.2)
Abscess NOS	0	1 (<0.1)
Abscess intestinal	0	1 (<0.1)
Appendiceal abscess	0	1 (<0.1)
Appendicitis	0	1 (<0.1)
Bacteraemia	0	1 (<0.1)
Bronchopneumonia NOS	0	1 (<0.1)
Cytomegalovirus infection	0	1 (<0.1)
Gastroenteritis viral NOS	1 (0.2)	1 (<0.1)
Prostatitis	0	1 (<0.1)
Psoas abscess	0	1 (<0.1)
Purulent discharge	0	1 (<0.1)
Salpingitis NOS	0	1 (<0.1)
Septic shock	0	1 (<0.1)
Staphylococcal sepsis	0	1 (<0.1)
Vaginal abscess	0	1 (<0.1)
Vulval abscess	0	1 (<0.1)
Cellulitis	1 (0.2)	0
Herpes simplex	1 (0.2)	0
Peritoneal abscess	1 (0.2)	0
Rectal abscess	2 (0.4)	0
Sepsis NOS	2 (0.4)	0
Tooth abscess	1 (0.2)	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.

SOURCE: TYSABRICD/SU3_CD/CSR/CP-SERINF.SAS DATE: 28MAR2006

Table 27 Short- and Long-Term Dosing in CD: Incidence of Serious Infections Experienced by >1 Subject

Preferred Term	Subject Who Received 1 or More Infusions From 1st Infusion to Start of 7th Infusion	Subject Who Received 7 or More Infusions From 7th Infusion to Start of 13th Infusion	Subject Who Received 13 or More Infusions From 13th Infusion to Start of 19th Infusion	Subject Who Received 19 or More Infusions From 19th Infusion to Start of 25th Infusion	Subject Who Received 25 or More Infusions From 25th Infusion to Start of 31st Infusion	Subject Who Received 31 or More Infusions From 31st Infusion Onwards
Number of Patients Dosed	1563 (100)	681 (100)	509 (100)	427 (100)	294 (100)	81 (100)
Number of Patients With an Event	33 (2.1)	17 (2.5)	5 (1.0)	6 (1.4)	2 (0.7)	1 (1.2)
Event						
Perianal abscess	7 (0.4)	4 (0.6)	1 (0.2)	0	0	0
Gastroenteritis NOS	3 (0.2)	1 (0.1)	2 (0.4)	1 (0.2)	0	0
Abdominal abscess NOS	2 (0.1)	1 (0.1)	0	2 (0.5)	0	0
Bacteraemia	2 (0.1)	0	0	0	0	0
Gastroenteritis viral NOS	2 (0.1)	1 (0.1)	0	0	0	0
Meningitis viral NOS	2 (0.1)	0	0	0	0	0
Appendicitis	1 (<0.1)	0	0	0	1 (0.3)	0
Herpes zoster	1 (<0.1)	0	1 (0.2)	0	0	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term under each column.
3: Preferred terms are presented by decreasing incidence in the first column.

SOURCE: TYSABRICD/SU3_CD/CSR/ADHOC/LT-SERINF-GT1.SAS DATE: 04APR2007

Table 27 Short- and Long-Term Dosing in CD: Incidence of Serious Infections Experienced by >1 Subject (cont'd)

Preferred Term	Subject Who Received 1 or More Infusions From 1st Infusion to Start of 7th Infusion	Subject Who Received 7 or More Infusions From 7th Infusion to Start of 13th Infusion	Subject Who Received 13 or More Infusions From 13th Infusion to Start of 19th Infusion	Subject Who Received 19 or More Infusions From 19th Infusion to Start of 25th Infusion	Subject Who Received 25 or More Infusions From 25th Infusion to Start of 31st Infusion	Subject Who Received 31 or More Infusions From 31st Infusion Onwards
Pneumonia NOS	0	1 (0.1)	1 (0.2)	0	1 (0.3)	0
Rectal abscess	0	1 (0.1)	0	1 (0.2)	0	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term under each column.
3: Preferred terms are presented by decreasing incidence in the first column.

SOURCE: TYSABRICD/SU3_CD/CSR/ADHOC/LT-SERINF-GT1.SAS DATE: 04APR2007

3.7.2.1 Pneumonia

The overall rate of pneumonia in placebo-controlled studies of CD was higher in natalizumab-treated patients compared with placebo-treated patients: 14.11/1000 patient-years in natalizumab (95% CI: 5.20/1000 to 30.46/1000) *vs* 5.55/1000 patient-years in placebo (95% CI: 0.14/1000 to 30.55/1000) (Table 29). However, the absolute number of cases of pneumonia was low (6 in natalizumab-treated patients and 1 in placebo-treated patients) and duration of exposure was also low, possibly leading to inaccurate estimates of true incidence and rate figures.

Table 28 Placebo-Controlled Studies of CD: Rate of Pneumonia

Preferred Term	Placebo	Natalizumab
Number of Patients Dosed	506	1182
Total Person-Years	180.09	425.19
Total Number of Pneumonia	1 (5.55)	6 (14.11)
Event		
Pneumonia NOS	1 (5.55)	4 (9.41)
Bronchopneumonia NOS	0	2 (4.70)

NOTE 1: Entries are number of events (event rate). Event rate = (total number of events / total person-years) X 1000.
2: Preferred terms are presented by decreasing rate in the Natalizumab column.
SOURCE: TYSABRICD/SU3_CD/CSR/CP-PNEU-RATE.SAS DATE: 13APR2006

3.7.3 Additional Infections of Note

3.7.3.1 Herpes Family Viral Infections

The incidence of infections in the family of herpes viruses from the placebo-controlled studies of MS and CD are shown in Table 29. The incidence of herpetic infections was slightly higher in natalizumab-treated patients than in placebo-treated patients (natalizumab *vs* placebo: 7.2% *vs* 6.1% for MS; 1.8% *vs* 1.2% for CD) (Table 29). There were no differences in the number of patients with Epstein-Barr virus infections (i.e., mononucleosis). Cytomegalovirus (CMV) is discussed separately below.

There were four reports of serious herpes infections in the CD trials, all in natalizumab-treated patients. Two patients were treated with intravenous acyclovir for dermatomal herpes zoster and one patient received acyclovir for herpes vaginitis. The fourth patient, who received natalizumab in a maintenance CD study, developed a primary varicella pneumonia following varicella exposure from her son who had contracted chicken pox. She recovered fully following intravenous acyclovir treatment. There were no reports of

disseminated herpetic infection, herpes meningitis, or herpes encephalitis in natalizumab clinical trials.

Prior to the suspension of marketing in 2005, there were two post-marketing reports of serious herpes infections in the CNS in natalizumab-treated MS patients. The first was a fatal case of herpes simplex encephalitis that occurred 3 months after a single dose of natalizumab. The second was a case of herpes simplex meningitis that developed several hours after a single dose of natalizumab. This patient recovered fully with acyclovir treatment. There were no OI's that have occurred during the post-marketing experience since re-introduction through 23 May 2007 (see Section 3.12).

Table 29 Placebo-controlled Studies of MS and of Treatment of Active CD: Incidence of Herpes Family Viral Infections

	Multiple Sclerosis		Crohn's Disease	
	Placebo	**Natalizumab**	**Placebo**	**Natalizumab**
Number of patients dosed	1135 (100.0)	1617 (100.0)	506 (100.0)	1182 (100.0)
Number of patients with a herpes family viral infection	69 (6.1)	116 (7.2)	6 (1.2)	21 (1.8)
Exact 95% CI for proportion	4.8, 7.6	6.0, 8.5	0.4, 2.6	1.1, 2.7
Herpes simplex	53 (4.7)	80 (4.9)	4 (0.8)	15 (1.3)
Herpes zoster	16 (1.4)	33 (2.0)	1 (0.2)	4 (0.3)
Herpes viral infection NOS	4 (0.4)	5 (0.3)	0	1 (<0.1)
Cytomegalovirus hepatitis	0	1 (<0.1)	0	0
Infectious mononucleosis	0	1 (<0.1)	0	0
Cytomegalovirus infection	1 (<0.1)	0	0	1 (<0.1)
Herpes simplex ophthalmic	1 (<0.1)	0	0	0
Mononucleosis heterophile test positive	0	0	1 (0.2)	0

NOTE: Numbers in parentheses are percentages. A patient was counted only once within each term.

NOS: Not otherwise specified.

CMV reactivation can occur in the setting of immunosuppression, so CMV infections were analyzed separately in both the placebo-controlled and open-label experience in MS and CD.

In the CD experience, there were 4 cases of CMV infection, two of which were serious atypical infections (CMV infection of the colon, CMV infection) that are described in Section 3.7.3.2. The other 2 cases were both non-serious cases of CMV hepatitis. In the placebo-controlled experience for CD, the incidence of CMV infections in CD was 0.08% (95% CI: 0.00%, 0.47%) in natalizumab-treated patients compared to no CMV infections in the placebo-treated patients (95% CI: 0.00%, 0.73%); the incidence was

0.26% (95% CI: 0.07%, 0.65%) when the open-label experience is included. Given the small number of cases (one case in the natalizumab treated group compared to none in the placebo-treated group, 3 patients in the open-label experience), conclusions regarding relationship to natalizumab are difficult.

In the MS placebo-controlled experience, there was one non-serious CMV infection in the placebo group (incidence of 0.09%; 95% CI: 0.00%, 0.49%) and one non-serious primary CMV hepatitis in a natalizumab-treated subject (incidence of 0.06%; 95% CI 0.00%, 0.34%); thus the incidence of CMV infections in both natalizumab and control groups were similar. There was an additional patient who developed elevated liver function tests reported as a serious adverse event following her second infusion of natalizumab in the setting of concomitant use of interferon beta-1a during the MS open-label experience. Subsequent ELISA testing was positive for IgM to CMV.

3.7.3.2 Opportunistic and Other Uncommon Infections

As with other biologic therapies used to treat inflammatory disorders, OI's have been observed in patients receiving natalizumab. These have occurred more commonly in patients with CD in association with significant co-morbidities or immunocompromise due to immunosuppressant use than in patients with MS. No opportunistic infections were observed in patients who received placebo.

In total, 5 OI's (excluding the 3 PML cases discussed in Section 3.7.3.3) were noted in patients on natalizumab treatment from more than 3000 patients evaluated in the CD and MS clinical trial programs. Of these 5 cases, 4 occurred in CD patients exposed to natalizumab (Table 30): *Mycobacterium avium intracellulare* complex pneumonia, bronchopulmonary aspergillosis, *Pneumocystis carinii* pneumonia, and *Burkholderia cepacia* bronchial infection. The remaining case, gastrointestinal cryptosporidiosis, occurred in an MS subject exposed to natalizumab.

The case of pulmonary aspergillosis occurred in a 73-year-old man with CD who developed peritonitis following a perforated duodenal ulcer 1 month after his last infusion of natalizumab. He had received a total of 11 natalizumab infusions and was taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and high dose prednisolone (50 mg daily). After several weeks in the hospital requiring ICU support, a CT scan showed bilateral infiltrates, and sputum cultures grew aspergillus. He subsequently died.

The case of PCP occurred in a 69-year-old man with CD who was hospitalized for hepatic encephalopathy, acute renal failure (ARF), and anemia. The subject had a history of cirrhosis with esophageal varices and ascites prior to study entry. He received his 34th infusion of natalizumab 1 month prior to developing hepatic encephalopathy. Two months after the last dose of natalizumab, he developed acute renal failure, pulmonary edema, and sepsis requiring intubation. Sputum was positive for *pneumocystis carinii* and he eventually died of sepsis.

The case of MAC pneumonia occurred in a 65-year-old woman with CD with a history of use of high-dose oral corticosteroids (prednisone 60 mg per day), although this had been tapered to 5 mg per day prior to the event. She initially presented after her fifth infusion of natalizumab with a non-productive cough and sinus infection, which was treated empirically with azithromycin. Her symptoms did not improve over the next month, and bronchoalveolar lavage revealed MAC by acid-fast bacilli (AFB) stain. Sputum cultures grew *Staphylococcus aureus*. She discontinued natalizumab and was treated with rifabutin, ethambutol, ciprofloxacin, and azithromycin. She made a full recovery.

The case of *Burkholderia cepacia* occurred in a 62-year-old woman with a history of tobacco use, Type II diabetes mellitus and hypertension, who was hospitalized for a nonproductive cough, dyspnea, and symptoms of congestive heart failure one month after her third infusion of natalizumab. She was taking prednisone 20 mg (last dose in January 2005), pentasa, folic acid, verospirone, hydrochlorothiazide, helicade, glimepiride, dilatrend, mucosolvan, tritrace, furosemide, and allopurinol. Chest X-ray revealed cardiomegaly, hydrothorax, and congestion in the pulmonary vessels. Ultrasound confirmed congestive failure. A spiral CT of the lungs revealed an effusion on the right side and fluid in the pleural cavity. A repeat CT scan 12 days later noted a wide band of residual atelectactic condensation in the right middle lobe and the central part of the basal segment of the lower lobe. The subject was treated empirically on oral amoxicillin/clavulanate and ciprofloxacin. Bronchoscopy and lavage were undertaken and the microbe *Burkholderia cepacia* was identified. Antibiotic therapy was continued until June 2005 and the patient recovered. The bronchial infection was considered to be secondary to cardiac failure and hospitalization.

The overall incidence of serious OIs across the combined placebo-controlled and open label CD experience (including the PML case) was 0.3% with a rate of 0.0028 per person-years of natalizumab exposure (95% CI: 0.0009 to 0.0066).

From the placebo-controlled MS experience, one patient experienced cryptosporidium diarrhea, which the investigator felt was prolonged due to natalizumab treatment. The event of cryptosporidium diarrhea occurred in a 31-year-old male who had received 17 natalizumab infusions. He was admitted to the hospital after a 10-day history of diarrhea and abdominal pain. Stool cultures were positive for cryptosporidium. The subject responded well to conservative measures, including rehydration. The event was considered resolved 70 days after his symptoms first started. Crytosporidial infections do occur in immunocompetent hosts and, in general, the infection is a self-limited illness with an average time to recovery ranging from several days up to 5 weeks (Leav *et al*, 2003). Based upon this case, in the placebo-controlled MS studies, the incidence of OI's in the natalizumab group was 0.12% (95% CI: 0.01%, 0.45%).

The rate of serious OIs (including PML) in MS patients receiving natalizumab in the placebo-controlled experience was 0.0007 (95% CI: 0.0001, 0.0025) infections per person-year. When the open-label natalizumab experience in MS is added (the second

patient with PML is included in the calculation), the overall incidence of OI's is 0.13% (95% CI: 0.03%, 0.38%) and the rate is 0.0008 (95% CI: 0.0002, 0.0023) per person-year, similar to the incidence and rate from the placebo-controlled experience.

There were 7 additional cases (6 CD; Table 30, 1 MS) of serious atypical infection in natalizumab-treated patients. These reports include primary varicella pneumonia following varicella exposure from an infected son; cavitating pneumonia with lung abscess; cytomegalovirus (CMV) colitis, and *Candida* sepsis in a subject on hemodialysis, 4 months after her last infusion. In addition, there was one report each of suspected tuberculosis (TB) of the abdomen and CMV infection 5–6 months after receiving the last dose of natalizumab; the treating physician ascribed the latter case to 6-MP. One MS subject also developed a serious CMV infection. Case histories for the CMV colitis and suspected TB case occurring in CD patients are provided below. Approximately half of these infections occurred in the setting of concurrent immunomodulatory or immunosuppressant therapies while others occurred in the setting of co-morbid illnesses.

One atypical CMV infection of the colon occurred in a natalizumab treated patient from the placebo-controlled CD experience. A CMV infection of the colon occurred in a 33-year-old woman 80 days after her second dose of natalizumab, which she was taking concomitantly with azathioprine. The patient reported a 10-day history of fever and night sweats and was admitted for evaluation. Endoscopic biopsy revealed an increase in chronic inflammatory cells, consistent with CD. However, PCR for CMV DNA was positive. Approximately 2 weeks later, the CMV infection resolved spontaneously and the subject was discharged from the hospital.

In the case of suspected peritoneal tuberculosis, the TB was discovered during abdominal surgery in a male patient with worsening CD 7 months after his last natalizumab infusion. Although pathology was suspicious for this diagnosis, all AFB stains and cultures were negative. Concomitant medications at the time of the event included azathioprine, which he had been receiving since 2003.

Table 30 Opportunistic and Atypical Infections in CD Clinical Experience

Infection	Diagnosis	Age/Gender	# of Infusions	Potential Confounders	Outcome
Opportunistic Infections	MAC infection	65/F	8	Prednisone / *S. aureus* pneumonia	Recovered
	PCP	69/M	34	Cirrhosis, ARF, sepsis	Death
	PML	60/M	8	AZA / lymphopenia	Death
	Pulmonary aspergillosis	73/M	11	Prednisolone / GI bleed, prolonged hospitalization	Death
	Burkholderia cepacia pneumonia	62/F	3	Tobacco use, CHF	Recovered
Atypical Infections	CMV colitis	33/F	2	Azathioprine	Recovered
	Varicella pneumonia	30/F	8	Primary infection in adult after son had chicken-pox	Recovered
	TB peritonitis	20/M	22	Caseating granuloma; neg AFB, neg culture	Recovered
	CMV infection	33/M	1	6-MP	Recovered
	Candida sepsis	48/F	1	Multi-organ failure	Recovered
	Cavitating pneumonia	32/M	13	Azathioprine, corticosteroids	Recovered

MAC pneumonia = *Mycobacterium avium intracellulare* complex pneumonia, PCP = *Pneumocystis carinii* pneumonia, PML = progressive multifocal leukoencephalopathy, TB = tuberculosis, CMV = cytomegalovirus, ARF = acute renal failure, CHF = congestive heart failure, AFB = acid-fast bacilli

3.7.3.3 Progressive Multifocal Leukoencephalopathy

BACKGROUND ON PML

PML is an infectious disease of the central nervous system caused by infection of oligodendrocytes by the JC virus (JCV). JCV is a human polyoma virus that is believed to infect the majority of healthy individuals at an early age. The seroprevalence of anti-JCV antibodies in healthy individuals has been estimated to range from 20% to 80% depending upon the testing methodology being used (Knowles *et al*, 2003; Knowles and Sasnauskas, 2003).

PML occurs predominantly in immunocompromised individuals with an age-adjusted death rate due to PML of 3.3 per million persons (in 1994), 89% of whom were AIDS patients (Holman *et al*, 1998). However, rare PML cases have also been reported in patients with autoimmune disorders who received immunosuppressive therapy; among

these, three patients with RA (Sponzilli *et al*, 1975; Rankin *et al*, 1995; Durez *et al*, 2002), one of whom was treated with tumor necrosis factor (TNF) antagonist (Durez *et al*, 2002). There was also a report of PML in a CD patient, but the concomitant treatments were not specified (Garrels *et al*, 1996). Additionally, PML has been reported in patients who have undergone organ transplants under treatment with concomitant immunosuppressive medication.

The exact mechanism by which PML develops is not known. It is hypothesized to be a stochastic process dependent upon multiple steps in the life-cycle of the JCV and its interactions with the immune system. The site of primary JCV infection is not known, but detection of JCV in tonsillar stromal cells and B lymphocytes may indicate a respiratory means of infection (Sabath and Major, 2002). The virus is also known to infect CD34+ hematopoietic precursor cells and kidney cell lines and is found in association with these tissues. One possible hypothesis is that following primary infection in the tonsil, JCV may traffic via B-cells from the primary source of infection to sites of latency in the kidney and bone marrow. This is supported by the identification of JCV in these tissues (Sabath and Major, 2002). The site of viral rearrangement and the mechanism by which the JCV enters into the brain from its sites of latency is also not known. It is hypothesized that systemic distribution of JCV may occur via direct hematogenous spread of virus or may be facilitated by B-lymphocytes and CD34+ precursor cells through low-affinity interactions of JCV with sialic acid residues on the surfaces of these cell types (Wei *et al*, 2000; Eash *et al*, 2004). JCV may eventually gain access to the brain via migration of these cells across the BBB or direct infection of the brain via interactions between JCV and 5HT2a receptors on the BBB (Elphick *et al*, 2004). Once in the brain, steps leading to lysis of oligodendrocytes and transformation of astrocytes are not understood.

The presence of JCV in the blood and urine of patients with PML and healthy, immunocompetent individuals has been described (Kitamura *et al*, 1990; Tornatore *et al*, 1992; Dorries *et al*, 1994; Sundsfjord *et al*, 1994; Agostini *et al*, 1996; Dubois *et al*, 1996; Knowles *et al*, 1999; Dorries *et al*, 2003). These findings however are neither predictive nor diagnostic of PML in these patients; thus the relationship of blood or urine viral load to PML is unclear.

The clinical presentation of PML is largely dependent upon the size and distribution of the white matter lesions that develop as a result of viral infection, demyelination, and glial cell lysis. About one-third of patients will present with visual field loss or cortical blindness with another third presenting with altered mentation or behavior changes (Dworkin *et al*, 2002). Hemiparesis is also a common presenting symptom. These symptoms are typically subacute in onset and follow a slowly progressive course. Often, patients and their families are the first to notice the onset of PML through changes in the ability to perform routine activities of daily living, even prior to presentation with changes on neurological examination.

MRI is a very sensitive tool for the detection of PML lesions in the setting of clinical signs or symptoms, although it lacks specificity. (Berger *et al*, 1998; Hoffmann *et al*, 2003; Langer-Gould *et al*, 2005). PCR analysis of the CSF for JC viral DNA is a highly sensitive and specific test for the diagnosis of PML. The specificity of this test approaches 100%, with a sensitivity ranging from 60% to 90% (Henson *et al*, 1991; Gibson *et al*, 1993; Weber *et al*, 1994a; Weber *et al* 1994b; Vago *et al*, 1996). In cases with a high clinical suspicion of PML and negative CSF results, repeat testing often leads to detection of JC viral DNA. As such, PCR analysis of the CSF for JC viral DNA is the preferred method for confirming the diagnosis of PML.

Untreated, PML patients have a mortality rate of 30% to 50% during the first 3 months (Koralnik, 2004). Prior to the introduction of highly active antiretroviral treatment (HAART) for HIV, about 10% of patients with PML survived for longer than 1 year. However, since the advent of HAART, about 50% of patients with PML survive for longer than 1 year due to restoration of immune function as CD4 counts increased, the so-called immune reconstitution inflammatory syndrome (Geschwind *et al*, 2001; Berger *et al*, 1998; Clifford *et al*, 1999; Tantisiriwat *et al*, 1999).

Currently, there is no established drug treatment for PML. Various medications have been tested, including acyclovir, idoxuridine, vidarabine, amantadine, adenine arabinoside, cytosine arabinoside (cytarabine), cidofovir, interferon α, interleukin-2 (IL-2), zidovudine, camptothecin, and topotecan (Koralnik, 2004; Dworkin *et al*, 2002; Seth *et al*, 2003; Collazos, 2003; Mamidi *et al*, 2002; Przepiorka *et al*, 1997; Redington *et al*, 2002; Padgett *et al*, 1983). However, the survival of patients with PML appears to be best correlated with immune reconstitution. In transplant patients with PML, early dosage reduction or/and discontinuation of immunosuppressive therapy was associated with favorable clinical outcome after PML diagnosis (Crowder *et al*, 2005; Shitrit *et al*, 2005).

SUMMARY OF THE THREE CONFIRMED CASES OF PML

The first patient was a 46-year-old female with MS who received 37 infusions of natalizumab in combination with interferon beta-1a. She began to experience motor dysfunction, cognitive and language difficulties, which progressed to right hemiparesis in December 2004. She received her last dose of natalizumab on 18 January 2005 and was admitted to hospital on 12 February 2005 with worsening clinical status. MRI showed extension of the lesions seen previously and extensive work-up revealed JC viral DNA in the CSF, leading to a diagnosis of PML. The patient died on 24 February 2005 and at autopsy, there was extensive cavitation in the left hemisphere as well as multiple non-cavitated, ovoid areas throughout the white matter of both hemispheres typical of PML (reactive astrocytes with enlarged, hyperchromatic nuclei). (Kleinschmidt-DeMasters and Tyler, 2005).

The second patient is a 46-year-old male with MS who exhibited behavioral changes followed by hemiparesis and cognitive impairment in November 2004. He had received interferon beta-1a in combination with natalizumab. His 29th and last dose of natalizumab was in December 2004. Despite treatment with high dose intravenous methylprednisolone, he continued to deteriorate and brain MRI in February 2005 demonstrated extension of a previously identified lesion. He underwent an extensive work-up, including CSF analysis and brain biopsy, which resulted in the diagnosis of PML. Approximately 3 months following discontinuation of natalizumab, he began to improve. At last report, he was able to converse but had significant residual cognitive impairment with left hemiparesis and ataxia. (Langer-Gould *et al*, 2005).

The final patient was a 60-year-old male with a history of CD for 28 years (Van Assche *et al*, 2005). He had been treated with azathioprine, oral budesonide, corticosteroids, and four doses of infliximab. The patient had evidence of lymphopenia and anemia since 1996. Azathioprine was commenced in 1999. He initiated natalizumab as part of CD 301 in March 2002 and received three doses concomitantly with azathioprine prior to being randomized to placebo in CD303. He remained on azathioprine and placebo until November 2002 when azathioprine was discontinued due to refractory pancytopenia. In February 2003, he began open-label treatment with natalizumab. In July 2003, he presented 1 month after his fifth dose of natalizumab with a 1-week history of cognitive decline. Brain MRI scan demonstrated a large T2-hyperintense lesion in the right frontal lobe, and additional hyperintense lesions in the left frontal and temporal lobes. He underwent a partial resection of the lesion, the pathology of which was read as an anaplastic astrocytoma, WHO Grade III. He deteriorated clinically and died in December 2003. As a result of the cases of PML in MS, the sponsors initiated a reassessment of the case and a diagnosis of PML was made following consultation with two independent neuropathologists.

In summary, three confirmed cases of PML have been identified: two MS patients and one CD patient. Both MS patients received natalizumab for over 2 years in addition to interferon beta-1a. The CD subject received eight doses of natalizumab over an 18-month period and was immunocompromised as evidenced by persistent lymphopenia. All three patients presented with subtle clinical changes early in their disease course that were noted by the patients or their families.

REVIEW OF THE SAFETY EVALUATION PROCEDURE

In collaboration with regulatory authorities in the US and Europe, the sponsors performed a comprehensive evaluation of patients exposed to natalizumab to systematically assess whether any had evidence of incipient PML or other OI.

The comprehensive safety evaluation assessed 3,430 patients (90% of those eligible) (2046/2248 MS, 1384/1571 CD/RA) and no additional confirmed cases of PML were found. Vital status was confirmed in 99% of these patients, making it unlikely that any

cases of PML were missed. The incidence of PML amongst patients treated with natalizumab in clinical trials in MS and CD is therefore approximately 1/1,000 with a 95% CI ranging from 0.2 to 2.8/1,000. Plasma testing proved to be neither predictive, nor diagnostic of PML, consistent with the published literature (Kitamura *et al*, 1990; Tornatore *et al*, 1992; Dorries *et al*, 1994; Sundsfjord *et al*, 1994; Agostini *et al*, 1996; Dubois *et al*, 1996; Knowles *et al*, 1999; Dorries *et al*, 2003). Indeed clinical and MRI abnormalities were present in two of the three patients with PML before JC viral DNA was detected in the plasma. In addition, JC viral DNA was detected in plasma in several patients in the study who had no clinical or radiographic signs of PML, including three who had never received natalizumab. These results suggest that, plasma JCV testing is not useful in predicting the likelihood of PML in asymptomatic patients. Physicians and patients should remain vigilant for signs and symptoms of PML and have a low threshold to suspend treatment and initiate appropriate diagnostic work-up (MRI, CSF analysis) in natalizumab-treated patients presenting with new neurological decline.

SUMMARY OF OPPORTUNISTIC INFECTIONS, INCLUDING PML

Serious OI's were observed in the natalizumab clinical program. The most frequent type of serious OI was PML, of which there were three confirmed cases that are discussed in Section 3.7.3.3. More patients with CD experienced OI's than in MS, where the only non-PML opportunistic infection seen was a case of cryptosporidial diarrhea. This is most likely due to differences in co-morbidities and concomitant medications used in patients with CD but not those with MS. The 0.3% incidence of OI's observed in the CD patients in these studies was comparable to that observed in CD patients in studies of TNF-α inhibitor therapies. In a population-based cohort study from Stockholm County, Sweden, of 217 patients with IBD, 2 (0.9%) developed severe OI's (Ljung *et al*, 2004). In a study of 500 patients treated with TNF-α inhibitor therapies, there were three cases (0.6%) of OI's (Colombel *et al*, 2004). While it is likely that natalizumab was a factor in the OI's in the studies of natalizumab, it is reasonable to suspect that co-morbidities and concomitant medications may have also played a potential role.

3.8 LABORATORY ABNORMALITIES

Consistent with its mechanism, lymphocyte counts increased within 2 weeks of the first natalizumab dose in CD patients (mean levels never exceeded the ULN). As well as lymphocytes, more natalizumab-treated than placebo patients had shifts to high values for total WBC, monocytes, eosinophils and basophils. The reversibility of the effect was demonstrated following discontinuation of natalizumab treatment. A percentage of placebo-treated CD patients had a shift to low lymphocyte count that may be due in part to concomitant use of steroids and other immunosuppressants by CD patients. Increased neutrophil count with natalizumab was observed in some CD patients but this is unlikely to be due to natalizumab, because a similar increase occurred in placebo-treated CD patients.

In CD, a higher proportion of natalizumab-treated patients than placebo patients had shifts from baseline to low values for red blood cells (25% *vs* 21%), hemoglobin (25% *vs.* 20%) and hematocrit (24% *vs.* 18%). Anemia is associated with active CD and it occurred slightly less frequently in natalizumab-treated CD patients than placebo patients. There were 10 serious cases of anemia in CD occurring in 8 patients who were receiving natalizumab. Of these 10 cases, all were related either to CD worsening or to bleeding from an ulcer; none were considered to be drug-related or required discontinuation of study drug. There were no events suggesting hemolysis.

Nucleated red blood cells (nRBCs) and precursor cells of neutrophil lineage (myelocytes and metamyelocytes) were detected in the peripheral blood of a minority of natalizumab-treated CD patients. These cells were present transiently and in small numbers; no association with anemia was noted. This finding is a normal consequence of the inhibition by natalizumab of α4-integrin binding on bone marrow stroma (Arroyo *et al* 1996). Expert opinion was that these effects on nRBCs and other progenitor cells are of no clinical significance (Spivak 2003).

There were no notable abnormalities in any other laboratory values associated with natalizumab treatment, including tests of hepatic or renal function.

3.9 IMMUNOGENICITY

In the Phase 3 studies, anti-natalizumab antibody responses were categorized as "transiently" antibody-positive or "persistently" antibody-positive. Transiently antibody-positive patients had detectable anti-natalizumab antibodies at a single time-point and were antibody-negative at subsequent time-points. The formation of transient antibodies to protein is a common occurrence and is likely due to the formation of IgM or transient low affinity IgGs (Smith *et al*, 1997; Wabl *et al*, 1999). Transient antibodies had no impact on safety. In an analysis of pooled data from Studies CD301, CD303, CD306, CD307, and CD351, 130 (10%) of 1,258 evaluated natalizumab-treated patients had a positive anti-natalizumab antibody titer at least once during the studies of whom 107 (9%) were considered persistently positive. The term persistently positive had originally been defined in the long-term MS studies as either one positive test that was reproducible on retesting at least 6 weeks later or a single positive test for a subject for whom no follow-up sample was available. However, the design of the CD short-term studies primarily used only a 12-week treatment period with only a single antibody test at study end. Therefore, a large number of patients with a single positive antibody test were considered to have persistent antibodies by the above definition. This could result in a falsely high proportion of antibodies being considered persistent, based purely on a definition that was best suited for long-term studies. When the persistent antibody analysis is modified and restricted to only patients with at least 2 antibody tests, persistent anti-natalizumab antibodies developed in only 5% of patients. Patients persistently positive for anti-natalizumab antibodies experience a loss of efficacy and increase in hypersensitivity reactions.

3.10 SAFETY IN SUBGROUPS

Adverse events were examined by gender, race, body weight, concomitant disease and geographic region to determine whether the 300 mg fixed dose of natalizumab was safe in these populations. There appeared to be no consistent pattern of risk associated with any of these intrinsic and extrinsic factors and natalizumab treatment. Increased diarrhea, arthralgia, depression, and nausea were more common in CD patients with increased weight. Other events occurred most commonly in the highest and lowest extremes of body weight, although not consistently so. There did not appear to be an increased risk for AEs with natalizumab compared with placebo treatment in low weight individuals. Also, there were no concomitant diseases, including a history of immunological disease, that increased the risk of more serious events, such as hypersensitivity-like reactions.

Natalizumab was not specifically studied in patients over age 65, in patients with renal and hepatic impairment, or in pediatric patients. Because natalizumab is a protein and thus not metabolized, renal or hepatic impairment are not expected to alter the pharmacokinetics of natalizumab.

In summary, the safety profile of natalizumab appeared to be similar in each of the subgroups examined.

3.11 DRUG INTERACTIONS

3.11.1 TNF-α Inhibitors (infliximab)

As the mechanism of natalizumab differs from approved biological agents used to treat Crohn's disease, and that combination therapies might be considered, a short-term study (CD 306) was conducted to assess whether there were any interactions between natalizumab and infliximab. In this study, natalizumab (300 mg) or placebo was added at Weeks 0, 4, and 8 to infliximab therapy (5 mg/kg at Weeks -2, and 6) in 79 CD patients (52 randomized to natalizumab) who were not in remission despite infliximab treatment. The most commonly reported adverse events were headache (23% natalizumab *vs* 22% placebo), fatigue (13 *vs* 7%), Crohn's disease (10 *vs* 15%), nasopharyngitis (10 *vs* 11%), and nausea (10 *vs* 11%).

One subject in each of the two treatment groups experienced a serious adverse event. One subject in the natalizumab group had a moderate exacerbation of CD with a small intestinal obstruction of moderate severity on Day 14. The subject discontinued the study due to the event. One subject in the placebo group had a severe bowel obstruction on Day 18. Neither serious adverse event was considered by the investigator to be related to study drug. Acute hypersensitivity-like reactions were reported in four patients in the placebo group within 2 hours of starting an infusion of infliximab. All four tested positive for human anti-chimeric antibodies (HACA). There were no hypersensitivity-like reactions in the natalizumab plus infliximab group.

In summary, the types and incidences of AEs were generally similar for patients who received natalizumab plus infliximab or placebo plus infliximab in this short-term clinical trial. There was no evidence of a drug-drug interaction with the use of the 2 drugs at the same time, and there appeared to be no increased risk of immunogenicity towards either drug with the use of the two agents in combination. No safety concerns were detected with short-term concomitant use.

3.11.2 Interaction with Steroids and/or Immunosuppressants

Safety events were compared among patients receiving natalizumab or placebo alone or in conjunction with immunosuppressants and/or steroids in the short-term placebo-controlled treatment studies of active CD (Table 31). In addition, safety events were analyzed in the 24-month long-term open-label study CD351. As part of this analysis, serious events including serious adverse events, infections, infusion reactions, and malignancy, were analyzed by treatment group in conjunction with immunosuppressants and/or steroids. Immunosuppressants were defined using the WHO Drug Dictionary**.**

The most common events reported across both treatment groups were headache, nausea, abdominal pain NOS, Crohn's disease, nasopharyngitis, arthralgia, and fatigue. In general, the incidence of these common adverse events was marginally higher in the natalizumab than in the placebo recipients regardless of concomitant administration of immunosuppressants and/or steroids. Within the group receiving natalizumab, concomitant administration of immunosuppressants and/or steroids did not necessarily precipitate a higher frequency of adverse events compared with those who received natalizumab alone.

Table 31 Immunosuppressant (+I), Steroid (+S) or +I +S Use (Short-Term Placebo-Controlled CD Studies)

Number of Patients	Study Drug Alone	+I	+S	+I+S
Placebo (n=506)	154 (30.4%)	89 (17.6%)	154 (30.4%)	109 (21.5%)
Natalizumab (n=1182)	373 (31.6%)	205 (17.3%)	340 (28.8%)	264 (22.3%)
Adverse Events				
Placebo	83.8%	89.9%	84.4%	86.2%
Natalizumab	83.6%	86.3%	89.1%	91.3%
Serious Adverse Events				
Placebo	8.4%	6.7%	15.6%	25.7%
Exacerbation of CD	2.6%	1.1%	12.3%	18.3%
Non-CD SAE	5.8%	5.6%	3.3%	7.4%
Natalizumab	8.6%	13.7%	15.9%	23.5%
Exacerbation of CD	1.9%	2.0%	7.6%	12.5%
Non-CD SAE	6.7%	11.7%	8.3%	11.0%
Infections				
Placebo	33.8%	37.1%	37.0%	37.6%
Natalizumab	41.3%	40.0%	39.4%	40.5%
Serious Infections				
Placebo	1.3%	1.1%	1.3%	6.4%
Natalizumab	1.9%	3.9%	2.6%	1.9%
Serious Infusion Reactions				
Placebo[1]	0	0	0	1.1%
Natalizumab[1]	0.3%	0	0.4%	1.4%

Note: percentage incidence in each subgroup is based on the number of patients in that subgroup

+I = concomitant immunosuppressants (no steroids); +S = concomitant steroids (no immunosuppressants); +I+S = concomitant immunosuppressants and steroids

[1] Studies CD301 and CD307 only: placebo (n=431) and natalizumab (n=983)

Source: Summary of Clinical Safety, Section 5.3.5

3.11.2.1 Serious Adverse Events

The overall incidence of serious adverse events in natalizumab-treated patients was 14.9%. The most common serious event was Crohn's disease and was seen more commonly, both in natalizumab and placebo groups, in patients also receiving systemic steroids or systemic steroids and other immunosuppressants compared to monotherapy or in combination with other immunosuppressants. This may reflect a more refractory

patient population for combination therapy than monotherapy patients, although the combination with immunosuppressants is not entirely consistent with this hypothesis.

Excluding CD as an SAE, there is a suggestion that other SAEs may be slightly more common in natalizumab-treated patients also receiving immunosuppressants than those receiving placebo plus immunosuppressants.

3.11.2.2 Infections

The incidence of infections was similar in the natalizumab group regardless of immunosuppressant and/or steroid use, and was slightly higher than the comparable placebo-treated groups. The most common infection was nasopharyngitis, experienced by 14.2%, 14.1%, 10.7%, and 13.3% of patients in the four groups – monotherapy, steroids, immunosuppressives and steroids plus immunosuppressives.

Infections were seen in 33.8% of patients who received placebo, with slightly higher incidence values in those also receiving steroids plus either immunosuppressants or steroids compared to placebo alone.

The incidence of serious infections (Table 31) was slightly higher in patients who received natalizumab in combination with steroids (2.6%) or other immunosuppressants (3.9%) compared with patients who received natalizumab as monotherapy (1.9%). However, paradoxically, the incidence of serious infections in patients who received natalizumab in combination with both steroids and other immunosuppressants was identical to that of those who received drug as monotherapy.

The patients who took placebo in combination with steroids or other immunosuppressants presented a similar incidence of serious infections compared with patients who received placebo alone (1.3 *vs* 1.1 *vs* 1.3%), however, the incidence in those taking placebo in combination with both steroids and immunosuppressants was higher (6.4%).

In summary, in the short-term placebo-controlled CD experience, the incidence of infections was similar among patients receiving natalizumab alone or in combination with immunosuppressants, steroids, or both immunosuppressants and steroids. There is a slight suggestion of higher infection rate in natalizumab patients compared to placebo patients but the differences are small and of questionable clinical significance. Serious infections were infrequent and the incidence varied across groups based on use, or not, of concomitant immunomodulatory therapy with no discernible pattern of increased risk.

Safety data in the long-term extension Study CD351 in patients who used concomitant immunosuppressants, steroids or both is provided in Table 32.

With long-term treatment, the incidence of AEs was not increased by the use of immunosuppressants and/or steroids. SAEs appear to have a higher incidence with concomitant immunosuppressants, oral steroids or both compared with natalizumab

alone; this is largely accounted for by the increased occurrence of the most common SAE (exacerbation of CD).

A slightly greater proportion of patients in the natalizumab alone or N+I group experienced an infection compared with patients receiving N+S and N+I+S (54% and 61% *vs* 46% and 50%, respectively). The most frequent types of infection reported were those involving the upper respiratory tract (URTI). Reports of nasopharyngitis were the most frequent URTI (range 16 to 20% across all subgroups). There was no marked difference between subgroups in the incidence of individual AEs.

The incidence of serious infections reported in Study CD351 was low but was increased somewhat by use of immunosuppressants and steroids (6%) compared with the other groups (1 to 4%). All serious infections except gastroenteritis NOS were reported in ≤1% of patients in each subgroup of natalizumab treatment. The incidence of gastroenteritis NOS was higher in the N+I+S group (2%) compared with the natalizumab alone, N+I, or N+S (<1% in each subgroup).

Table 32 Immunosuppressant (+I), Steroid (+S) or +I +S Use (Study CD351)

	Natalizumab alone	+I	+S	+I+S
Number of Patients (n=1100)	480	269	223	128
Adverse Events	83%	84%	78%	73%
Serious Adverse Events	14%	17%	19%	21%
Exacerbation of CD	3%	6%	5%	7%
Infection	54%	61%	46%	50%
Serious Infections	3%	1%	4%	6%
Immunogenicity (Screening Antibodies; n=1090)	10%	3%	6%	2%
Infusion Reactions	11%	12%	11%	12%
Hypersensitivity-like reactions	4%	1%	2%	2%

Note: percentage incidence in each subgroup is based on the number of patients in that subgroup

+I = baseline immunosuppressants (no steroids); +S = baseline steroids (no immunosuppressants); +I+S = baseline immunosuppressants and steroids

Source: CD351, Sections 15.3.1 (Tables 3.3.1 to 3.3.8 and Table 3.10.6)

3.11.2.3 Conclusion

The data demonstrate that in short-term, placebo-controlled trials the overall safety of natalizumab is similar to placebo when used as monotherapy or in combination with immunosuppressants and/or steroids. Analysis of safety events by use of immunosuppressant and/or steroids in the short-term, placebo-controlled trials suggests that the overall safety of natalizumab is similar when used as monotherapy or in combination with immunosuppressants and/or steroids. However, given the overall low

incidence of serious infections in the studies, assessment of the risk for these events in natalizumab-treated patients receiving concomitant immunosuppressants and/or steroid is limited.

3.12 POST-MARKETING SAFETY

Between November 2004 and February 2005 (the first marketing phase in the US), approximately 7,500 patients were dosed with natalizumab in the post-marketing setting, representing approximately 900 person-years of exposure.

Natalizumab was approved for use in patients with relapsing MS in Europe in the US in June 2006 (second marketing phase in the US). Natalizumab is now licensed in 34 countries worldwide. From June 2006 until 23 May 2007, it is estimated that approximately 11,500 patients have been treated with natalizumab worldwide in the post-marketing setting, of which 8,313 have been treated in the US and approximately 3,200 in Europe. Of the 8,313 patients dosed in the US, 2,068 patients had been previously treated with natalizumab prior to February 2005. The total natalizumab exposure from June 2006 until 23 May 23 2007 is 3,800 person-years. Cumulative exposure in the post-marketing setting, including the November 2004 to February 2005 interval, is therefore approximately 16,000 patients and 4,700 person-years.

A detailed review of deaths, serious hypersensitivity reactions, malignancies, serious infections, serious hepatic dysfunction, serious hematological events, serious cardiac events, and serious CNS events was performed on data from June 2006 to 23 May 2007. The safety profile of natalizumab observed in the post-marketing setting is generally consistent with the adverse event profile observed in the clinical trial safety database.

The overall rate of hypersensitivity reactions, including serious hypersensitivity reactions and anaphylaxis, in the post-marketing setting is consistent with the clinical trial experience and current product labeling. Data analyzed in the US from June 2006 to 23 May 2007, indicate that the reporting rate of serious hypersensitivity reaction was 0.9%, which is consistent with the rate in MS clinical trials. The majority of these reactions occurred at the second dose. Of the cases of serious hypersensitivity reactions, 31 cases of anaphylaxis were reported; the reporting rate for these reactions was 0.4%, which is similar to the rate in MS clinical trials. There were no deaths due to anaphylaxis. Nineteen of the 31 cases of anaphylaxis occurred in patients previously exposed to natalizumab (reporting rate of 0.9%) and 9 were reported in those naïve to natalizumab (reporting rate 0.2%). (The prior natalizumab treatment status was unknown in 3 patients.) Antibody status for patients in the post-marketing setting is largely unknown. These data suggest that, similar to experience with other therapeutic monoclonal antibodies, patients who receive natalizumab treatment after an extended period without treatment may be at a higher risk of hypersensitivity reactions that patients who receive regularly scheduled therapy. Given that patients with persistent antibodies to natalizumab experience reduced efficacy, and that hypersensitivity reactions are more common such patients, consideration should be given to testing for the presence of

antibodies in patients who wish to recommence therapy following a dose interruption. The US product label has been modified (under Adverse Reactions) with this information.

The frequency and histological type of malignancies reported in the post-marketing setting is generally consistent with the general US and European population. The most common type of malignancy reported was breast cancer, which is not unusual given the female predominance in the MS population. There were 2 reports of low-grade follicular lymphoma, occurring after 1 and 5 doses of natalizumab treatment, respectively. One patient had a prior history of lymphadenopathy. Given the patients' short duration of natalizumab exposure and the low-grade nature of their lymphoma, it is unlikely these were causally related to natalizumab. Tumors typically associated with immunosuppression, such as high-grade lymphoma, Kaposi's sarcoma, or multiple melanoma skin cancers were not observed.

The pattern of infections in the post-marketing period is consistent with the clinical trial experience for natalizumab. The most common serious infections reported in the post-marketing setting were urinary tract infections and pneumonia. One case of herpes encephalitis, which resulted in death, and one case of herpes meningitis with full recovery, have been described previously in Section 3.7.3.1. Both events occurred during the period following the initial launch in November 2004 and are included in the US labeling for natalizumab. Importantly, there have been no new confirmed cases of PML or other OI's in the post-marketing setting worldwide since the re-introduction of natalizumab in June 2006 until 23 May 2007.

In conclusion, no cases of confirmed PML or OI's, or malignancies associated with immunosuppression were reported in the post-marketing experience. Apart from new findings regarding hypersensitivity reactions upon re-dosing after a dose interruption, the overall safety profile of natalizumab in the post-marketing experience is consistent with the safety profile in clinical trials.

3.13 SAFETY SUMMARY

The safety of natalizumab has been evaluated in approximately 3,900 patients, accounting for approximately 4,700 patient-years of exposure. In the placebo-controlled experience, 2,799 natalizumab-treated patients with MS and CD are included, accounting for 2,900 patient-years of placebo-controlled exposure. Based upon these analyses, it is possible to make several conclusions regarding the overall safety of natalizumab:

- Common and serious adverse events were similar in natalizumab-treated patients and control patients.
- The incidence of hypersensitivity in the short-term placebo-controlled CD trials was 3.5%. The incidence of serious hypersensitivity reactions in the pooled short- and

long-term studies in CD was less than 1% and these events were managed successfully.

- Approximately 5% of patients who received natalizumab in CD clinical studies developed persistent anti-natalizumab antibodies, which were associated with loss of efficacy and a higher incidence of infusion-related adverse events.
- The incidence of malignancy is increased in natalizumab-treated patients compared with placebo-treated patients in the short-term placebo-controlled CD studies. However, the time period for this assessment is short (≤16 weeks) and the confidence intervals are wide making an association with drug unlikely. In the longer-term MS placebo-controlled trials and in the pooled CD and MS experience, the incidence of malignancy is similar for natalizumab- and placebo-treated patients. It is recognized that malignancy signals may take years to evaluate adequately; thus the long-term incidence of malignancy in natalizumab-treated patients will be further evaluated in the CD observational study.
- The overall incidence and rate of common and serious infections were similar in natalizumab-treated patients and control patients.
- Concomitant therapy with immunosuppressants, corticosteroids or inhibitors of TNF-α were not associated with an increase in infection rate. Use of such combination therapy is not recommended due to the potential increased risk of PML.
- Serious opportunistic infections, including PML, occurred uncommonly in natalizumab-treated patients. Opportunistic infections were mostly observed in patients with CD, and in the majority of the cases, in association with concomitant immunosuppressant use or other significant co-morbidities.
- A comprehensive safety evaluation of natalizumab-treated patients confirmed that there were a total of three cases of PML, representing an approximate incidence of PML of 1 per 1000 (95% CI: 0.2 to 2.8 per 1000).

3.14 PATIENT SELECTION BASED UPON EFFICACY AND SAFETY

Natalizumab (TYSABRI®) has the following proposed indication for CD:

TYSABRI® is indicated for inducing and maintaining sustained response and remission, and eliminating corticosteroid use in patients with moderately to severely active Crohn's disease with inflammation, as evidenced by elevated CRP level or another objective marker.

Because TYSABRI® increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies.

Natalizumab is thus targeted as a potential therapy for patients with moderate to severe, active CD in whom objective evidence of inflammation (as defined by elevated CRP or other objective marker) is present. The drug is recommended for use only in patients who have failed therapy with conventional agents (steroids and immunosuppressant drugs). However, due to potential safety concerns, natalizumab is likely to be used initially in those patients who have also failed an inhibitor of TNF-α.

There are a few additional patient groups where the use of natalizumab may not be justified, either because data are lacking or because the benefit/risk ratio is altered:

- *Patients who are immunocompromised from any cause, including use of immunosuppressant medications.* Immunocompromised patients have an independent risk factor for PML and other opportunistic infections. Therefore, these patients should not receive natalizumab.
- *Patients who have previously suffered a hypersensitivity reaction to natalizumab.* Re-dosing of natalizumab following a hypersensitivity reaction was not assessed in the Phase 3 program. Until these data are available, all patients with infusion-related hypersensitivity reactions, defined as urticaria with or without associated systemic symptoms, should be discontinued from further natalizumab.
- *Patients who develop persistent antibodies to natalizumab.* Persistent antibodies against natalizumab lead to a loss of efficacy and an increase in infusion-related side effects. Prescribers should consider the overall benefits and risks of natalizumab in a patient with persistent antibodies.

3.15 CONCLUSION

Through detailed safety analyses, we have identified PML as a rare, but significant, risk. In addition, uncommon but serious non-PML opportunistic infections have been observed in natalizumab-treated CD patients, primarily in patients receiving concurrent immunosuppressants or with other significant co-morbidities. In addition, we have identified patient populations that should not receive this treatment, i.e., patients at higher risk of opportunistic infections due to immunosuppression or concomitant use of immunosuppressants. A comprehensive risk management program in the post-marketing setting will focus on appropriate use conditions and assessment and minimization of the risk of PML and other serious opportunistic infections. This is part of the Risk Management Action Plan proposed in Section 4.

4 RISK MANAGEMENT PLAN

Elan Pharmaceuticals and Biogen Idec (the Sponsors) have previously developed a comprehensive risk management plan (RiskMAP) to accompany use of TYSABRI in MS patients, consisting of both risk assessment and a risk minimization features. This plan, the TOUCH (TYSABRI Outreach: Unified Commitment to Health) Prescribing Program was developed in consideration of FDA's Guidance Document on this topic[3], and in consideration of the recommendations of the Peripheral and Central Nervous System Drugs Advisory Committee (Advisory Committee).

The existing TYSABRI RiskMAP for MS is designed to promote informed benefit-risk decisions between prescribers and patients regarding the use of TYSABRI in relapsing MS, to minimize morbidity and mortality due to PML through early detection with clinical vigilance, and to minimize the risk of PML by treating patients who are not immunocompromised and, consistent with the Prescribing Information (PI), warning against concurrent use with antineoplastics, immunosuppressants or immunomodulators, such as beta-interferons or glatiramer acetate. In addition, the plan seeks to determine the incidence and risk factors for PML and other serious OI's in patients treated with TYSABRI, as well as the overall safety of TYSABRI in the clinical practice setting.

Upon approval of TYSABRI for the treatment of moderately to severely active CD, it is proposed that the TOUCH Prescribing Program have two versions, one for MS patients (MS-TOUCH) and the other for CD patients (CD-TOUCH). The methods of the TYSABRI RiskMAP for MS patients will be adapted for Crohn's patients with minor modifications to accommodate differences in the treatment and management of moderate to severe CD. These changes include alteration of appropriate patient, physician and infusion site forms and communication tools to include and substitute (as appropriate) information on CD and use of TYSABRI in CD. The Sponsors have sought extensive feedback from neurologists to obtain their recommendations on how best to minimize the risk of PML, and surveyed many gastroenterologists, neurologists, CD and MS patients, infusion nurses and sites, and central pharmacies regarding the feasibility of the plan. The Sponsors have also developed a companion Quality Plan that outlines the monitoring of systems and compliance data generated by the RiskMAP in both CD and MS patients.

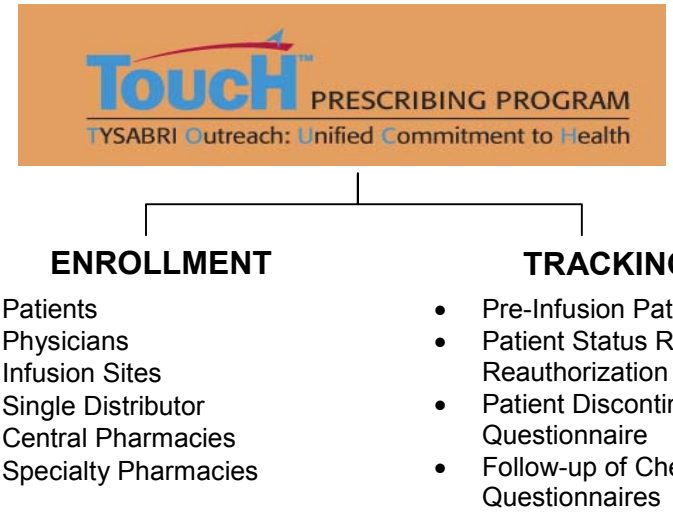
The TOUCH Prescribing Program (TOUCH program elements) features, among other things:

- Mandatory enrollment of all prescribers and patients into the TOUCH Prescribing Program, a registry that provides diligent safety surveillance and systematic tracking of all patients

[3] *See* FDA, Guidance for Industry -- Development and Use of Risk Minimization Action Plans (March 2005).

- Mandatory training and enrollment of all infusion sites, and all central pharmacies affiliated with authorized infusion sites, into the TOUCH Prescribing Program.
- Controlled distribution system for TYSABRI so that TYSABRI is delivered to and administered only in authorized infusion sites
- Mandatory completion of the Pre-Infusion Patient Checklist and distribution of the Medication Guide to each patient prior to each monthly TYSABRI dose
- Real-time submission of Pre-Infusion Patient Checklists to Biogen Idec to monitor infusion site compliance and to track TYSABRI dosing on a patient-specific basis
- Mandatory prescriber re-authorization of TYSABRI dosing for each patient every 6 months
- At the heart of the TOUCH Prescribing Program is an integrated, computerized, validated database that captures enrollment, patient tracking, and drug distribution data (Figure 8).

Figure 8 TOUCH Program Elements



The RiskMAP primarily seeks to minimize the risk of PML, a rare, but serious, adverse event without creating unintended consequences that may obstruct appropriate patient access to the potential significant benefits of TYSABRI. Since the re-introduction of TYSABRI into the US market for MS, Biogen Idec and Elan have been assessing the effectiveness of the RiskMAP and the information that it generates through a multi-disciplinary TYSABRI Risk Management Review Committee, reporting the outcomes to FDA, and will be acting promptly to revise and improve the plan, as necessary, in order to achieve its goals.

4.1 RISK MINIMIZATION

The goals of risk minimization are:

- **To promote informed benefit-risk decisions regarding TYSABRI use in MS and CD patients.** Prescribers and their patients should know that TYSABRI is associated with an increased risk of PML, which usually causes death or severe disability. Prescribers should also know that TYSABRI is indicated only for the treatment of relapsing MS and moderately to severely active CD.
- **To minimize the risk of PML.** To the extent possible, based on currently available data, patients who are already at risk of developing PML should not receive TYSABRI treatment. Patients who are immunocompromised are at increased risk of developing PML and, consistent with the PI, generally should not receive TYSABRI treatment. In addition, based on limited data, use of TYSABRI in combination with antineoplastic, immunosuppressant or immunomodulatory agents may further increase the risk of PML compared to TYSABRI monotherapy. Thus, prescribers should know that TYSABRI should not be used concurrently with antineoplastics, immunosuppressants or immunomodulators.
- **To minimize death and disability due to PML.** Although the data are limited, it is prudent to encourage early detection and immune-reconstitution in any patient who develops PML in order to potentially improve patient outcome. Thus, it is important that prescribers know how to diagnose PML and know to withhold TYSABRI dosing immediately at the first signs or symptoms suggestive of PML. Patients should know to promptly report to their prescriber any continuously worsening nervous system symptoms lasting over several days.

There are several important aspects about the medical management of patients with CD and the administration of TYSABRI that will allow for successful implementation of the CD Risk Minimization Action plan (RiskMAP).

1. TYSABRI will be prescribed in the treatment of CD by prescribers who specialize in the care of patients with CD and who have experience in the evaluation of patients with opportunistic infections

The targeted prescribers of TYSABRI for CD are primarily gastroenterologists who have experience in use of biological therapies, such as infliximab, and other immunosuppressant therapies, such as azathioprine. These therapies are infrequently associated with major toxicities, including serious, life-threatening, and opportunistic infections. Infliximab is also associated with rare episodes of demyelinating illness. As a result, gastroenterologists are familiar with recognition of symptoms related to OI's and neurological complications of therapy. They have established practices of referral to other specialists, including neurologists, for additional care as appropriate for the further

evaluation and treatment of their patients. The TYSABRI risk minimization strategy builds upon this existing knowledge base and referral pattern.

2. Discussion of risks and benefits associated with CD treatment is the standard of care in gastroenterology practice.

Prescribing a disease-modifying treatment for a serious, disabling disease such as CD is a carefully considered and deliberate decision. Surveys of CD patients have demonstrated that patients have well-defined preferences among treatment attributes and are willing to accept serious risks in exchange for clinical efficacy. Based upon feedback from gastroenterologists and CD patients, the decision to start a new therapy usually involves a detailed discussion between the prescriber and patient about the risks and benefits of available therapies. Some gastroenterologists already use an informed-consent form prior to initiating therapy with immunomodulatory or immunosuppressant agents for CD. The TYSABRI risk minimization strategy builds upon this existing decision-making process.

3. TYSABRI is administered monthly by healthcare professionals in infusion sites.

In contrast to therapies that are self-administered in the patient's home, TYSABRI is administered intravenously every month at an infusion site under the care and management of infusion nurses. For CD in particular, infusion-based therapies are widely available; this means that many infusion centers that administer therapies to CD patients will be already familiar with the care of CD patients. This regulated, procedure-oriented dispensing environment allows for monthly monitoring of patients for potential symptoms suggestive of PML and for effective dissemination of information on TYSABRI that reinforces appropriate use.

The TOUCH Prescribing Program is designed to inform prescribers, infusion nurses, and patients about the risk of PML and how to minimize that risk. A RiskMAP system of mandatory enrollment of all prescribers and patients, controlled distribution of TYSABRI, and administration of TYSABRI only in trained and authorized infusion sites was developed to build upon the unique aspects of the medical management of MS and CD patients and the administration of TYSABRI.

4.1.1 Prescribing, Enrollment, and Dispensing System

4.1.1.1 Mandatory Enrollment of Prescribers and Patients

A key feature of the RiskMAP is mandatory enrollment of all prescribers and patients into the TOUCH Prescribing Program as a prerequisite to prescribing or receiving TYSABRI treatment. CD patients will enroll into the CD-TOUCH Prescribing Program. Although, there will be CD and MS-specific versions of the Prescriber/Patient Enrollment Form, the enrollment process will be the same for both the CD-TOUCH and MS-TOUCH Prescribing Program.

4.1.1.1.1 Prescriber/Patient Enrollment Form

Prescribers and patients must complete and sign a mandatory Prescriber/Patient Enrollment Form and send it to the Sponsor prior to initiating TYSABRI treatment. There will be CD and MS-specific versions of the Prescriber/Patient Enrollment Form.

The purpose of the Prescriber/Patient Enrollment Form is to help assure that (1) both the prescriber and patient are informed of the known risks of TYSABRI, including the risk of PML, (2) TYSABRI is prescribed only for appropriate patients, and (3) that patients will be tracked longitudinally for safety outcomes.

The Prescriber/Patient Enrollment Form will be used to collect baseline demographic information including the prescriber's name and contact information, patient's name, contact information, age, gender, social security number, moderately to severely active CD diagnosis, most recent prior CD therapy; prior TYSABRI exposure; a TYSABRI prescription; and a Patient-Prescriber Acknowledgement.

On the Prescriber/Patient Acknowledgement, prescribers affirm by signature, among other things, that they are aware of the PML risk, that they have discussed the risks and benefits of TYSABRI with their patient, and that their patient is appropriate for TYSABRI treatment. Patients affirm by signature, among other things, that they have read the Medication Guide, that they have discussed the risks and benefits of TYSABRI with their physician, and that they will report any new or worsening neurological symptoms to their physician.

4.1.1.1.2 Enrollment Process for Prescribers and Patients

The enrollment process for CD will utilize the same system designed for MS. A complete list of prescribers and patients authorized in the TOUCH Prescribing Program is maintained in the TOUCH database.

The Sponsor reviews the submitted Prescriber/Patient Enrollment Form for completeness and accuracy, and verifies that both the prescriber and the patient have signed the form. The prescriber and patient information is entered into the TOUCH database. At that time, a unique Patient Enrollment Number is assigned to the patient in the TOUCH database, which remains the same for that patient, even if the patient de-enrolls and subsequently re-enrolls into the program. A case manager is assigned to the patient and the patient is matched to an authorized infusion site. Alternatively, the Sponsor confirms that the infusion site to which the prescriber has referred the patient is authorized in the TOUCH Prescribing Program.

The prescriber must complete and sign a new Prescriber/Patient Enrollment Form for every patient of his or hers that enrolls into the TOUCH Prescribing Program. In addition, after a patient has authorized, the prescriber must reauthorize TYSABRI use for that patient every 6 months.

4.1.1.2 Pre-Infusion Patient Checklists

Prior to each infusion, an authorized infusion site must verify that the patient is currently authorized to receive TYSABRI treatment from the medical record. In order to verify eligibility, the site must refer to the patient's medical record.

Only if the patient is authorized to receive TYSABRI, will the site next provide the patient with the TYSABRI Medication Guide, give the patient time to read the Medication Guide, and complete the Pre-Infusion Patient Checklist. The complete Pre-Infusion Patient Checklist must be submitted to the Sponsors within 1 business day of completion.

The Pre-Infusion Patient Checklist questions the patient about any new or worsening neurological symptoms or concurrent immunosuppressive therapies. If the patient reports such new symptoms or therapies, then the infusion nurse is instructed to withhold TYSABRI treatment and contact the patient's physician for further instruction. Thus, the Pre-infusion Patient Checklist is designed to minimize inappropriate use of TYSABRI, monitor for inappropriate use of immunosuppressive therapies that might increase the risk of PML and to facilitate early detection of worsening neurological symptoms that might be indicative of PML through regular, monthly assessments by infusion nurses at infusion sites.

4.1.2 Reauthorization Process for Every Patient Every 6 Months

The prescriber must explicitly reauthorize TYSABRI use for the patient every 6 months using the TYSABRI Patient Status Report and Reauthorization Questionnaire. In addition, on this questionnaire, the prescriber must provide information on the patient's vital status, whether the patient has developed PML or other serious OI's, and whether the patient has received any concurrent immunosuppressive or immunomodulatory therapies.

An appropriately completed questionnaire is a requirement for the patient to continue to receive TYSABRI treatment. In order for the prescriber to be able to complete this questionnaire, the Sponsor expects that the prescriber will have recently examined the patient.

If the patient discontinues TYSABRI treatment, the Prescriber must complete a Patient Discontinuation Questionnaire regarding the status of the patient 6 months after the patient's last dose of TYSABRI.

4.1.3 Controlled Centralized Distribution System for TYSABRI

A controlled distribution system has been designed to deliver TYSABRI only to infusion sites (or, if appropriate, their affiliated central pharmacies) that have been trained by the Sponsor's personnel on the known risks and appropriate use of TYSABRI, using

education tools[4], and have attested that they will follow the RiskMAP requirements. The controlled distribution of TYSABRI allows tracking of TYSABRI shipments, i.e., the location and number of all vials shipped to the infusion site. The controlled distribution system will be the same for both CD- TOUCH and MS-TOUCH.

Specialty pharmacy providers are organizations that dispense specialty products, including injectable and infusible therapies. Central pharmacies are distinct from specialty pharmacies. A central pharmacy is part of a hospital, group practice or infusion site, and is affiliated with one or more infusion sites.

Elan has contracted with a single distributor and a limited number of specialty pharmacies to distribute TYSABRI only to authorized infusion sites. The single distributor ships product only to authorized specialty pharmacies, central pharmacies or infusion sites. The single distributor and participating specialty pharmacies are contractually obligated to follow RiskMAP requirements with respect to the purchase and distribution of TYSABRI.

4.1.3.1 Mandatory Enrollment of Central Pharmacies

Central pharmacies that dispense TYSABRI to authorized infusion sites must also enroll in the TOUCH Prescribing Program. Retail pharmacies and wholesalers are excluded from holding and dispensing TYSABRI.

4.1.3.2 Mandatory Training and Enrollment of Infusion Sites

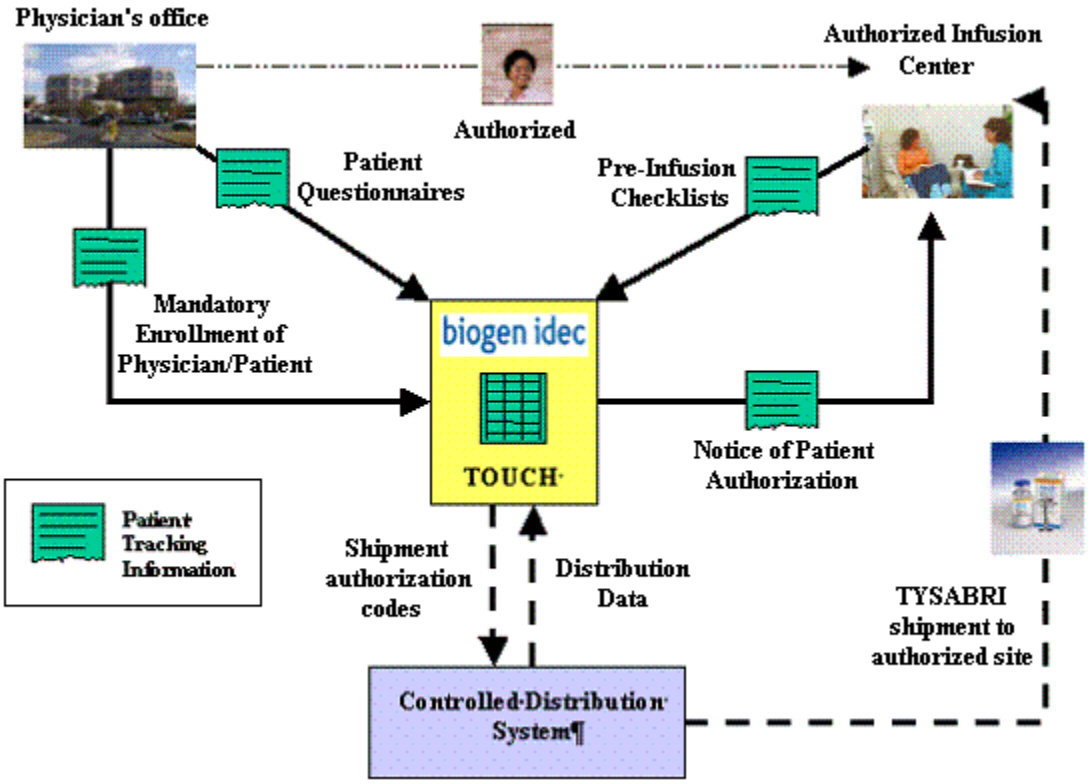
The TOUCH Program requires that TYSABRI is shipped only to and administered only at infusion sites authorized in the TOUCH Prescribing Program. Authorized infusion sites are sites that have been trained on the known risks, potential benefits and appropriate use of TYSABRI, using educational materials. The infusion sites must also agree to comply with the RiskMAP requirements.

4.1.4 TOUCH Prescribing Program: Summary of Patient Data Collection

At the heart of the TOUCH Prescribing Program is an integrated, computerized, validated database that captures enrollment, patient tracking, and drug distribution data, as presented in Figure 9.

[4] As requested by the FDA, prior to distributing education materials relating to the RiskMAP, all materials will be submitted for FDA review.

Figure 9 Data Collection in TOUCH Prescribing Program



All information from the Prescriber/Patient Enrollment Form, monthly Patient Pre-Infusion Checklists, Patient Status Report and Reauthorization Questionnaire, and Patient Discontinuation Questionnaires is collected by the Sponsor. This information includes details on the prescriber, patient, infusion site, TYSABRI dosing, use of other immunomodulatory or immunosuppressive therapy, presence of any worsening neurological symptoms or new medical conditions that could compromise immune function, as well as occurrence of PML or other OI's.

The database will also contain information related to the supply chain and distribution of TYSABRI through the controlled distribution system. This information will allow for the tracking of each prescription from the distributor to the intended infusion site and patient.

In addition to data above, the Sponsor collects the data through the course of diligence efforts (e.g., missing Pre-Infusion Patient Checklists).

Joint drug safety surveillance activities and exchange of safety information is regulated in a Safety Data Exchange Agreement between the Biogen Idec and Elan. Adverse events reported through the TOUCH Prescribing Program will be collected by the Sponsor and these adverse events, whether reported by a patient, prescriber, or other person, are

entered and tracked in Biogen Idec's Drug Safety's Global Database (Oracle AERS). Elan's Global Safety Surveillance department has access to this database for the purposes of review and reporting of CD-TOUCH related information.

4.1.5 Educational Tools for Prescribers, Patients, Infusion Sites, and Central Pharmacies

The Sponsors sought feedback from gastroenterologists, neurologists, infusion sites, infusion nurses, central pharmacies, CD and MS patients to develop materials that would be useful, effective, and practical for managing the risk of PML. Based upon this feedback, a number of tools have been developed that will educate healthcare providers, and thus their patients, about the potential risk for, and consequences of, PML with TYSABRI treatment. These materials will be used subject to FDA review and approval, to educate healthcare providers, and thus patients, of the known risks and potential benefits of TYSABRI treatment. These tools are distributed directly to the infusion sites and prescribers with subsequent dissemination to patients. Patients and healthcare providers can also access up-to-date information at the product's website, www.TYSABRI.com, and through a toll-free phone-line to a TYSABRI call center. Distribution of enrollment forms is controlled and available only from Elan and Biogen Idec directly. Materials that are essential to implementation of the risk management plan are listed in Table 33 below:

Table 33 RiskMAP Materials

Material	Brief Description
Patient Medication Guide	The Medication Guide describes the known risks of TYSABRI in patient-oriented language and is included with the package insert and is provided prior to every infusion.
TYSABRI and TOUCH Prescribing Program Slide set	PowerPoint presentation that includes clinical data and an overview of the TOUCH Prescribing Program elements, intended for physicians and patients (2 sections). This slide set will be updated to incorporate CD-TOUCH program elements.
TOUCH Prescribing Program Overview	General description of the TYSABRI risk management program outlining responsibilities for prescribers, infusion sites, central pharmacies, and patients.
Prescriber/Patient Enrollment Form	Form to be signed by all patients and prescribers for enrollment into the TOUCH Prescribing Program.
Infusion Site Enrollment Form	Form to be signed by infusion sites for enrollment into the TOUCH Prescribing Program and to obtain designation as an authorized infusion site. Only authorized infusion sites are eligible to receive TYSABRI shipments. Currently approved materials will be used.
Central Pharmacy Enrollment Form	Form to be signed by central pharmacies for enrollment into the TOUCH Prescribing Program and to obtain designation as an authorized central pharmacy. Only authorized central pharmacies are eligible to receive TYSABRI shipments and may dispense TYSABRI only to authorized infusion sites within their organization/ institution. Currently approved materials will be used.
TYSABRI Inventory Tracking Log	Tracking log required for use by central pharmacies to document dispensing of TYSABRI to authorized infusion sites associated to a central pharmacy. Currently approved materials will be used.
Pre-infusion Patient Checklist	Pre-infusion Patient Checklist to be used prior to each infusion for every patient on TYSABRI. Checklist must be submitted to Biogen Idec upon completion. A CD-TOUCH version will be developed. The currently approved version for MS will be re-named as the "MS-TOUCH Prescribing Program."
Patient Status Report and Reauthorization Questionnaire	Form that must be filled out every 6 months to obtain patient status and enable prescriber reauthorization of the patient in the TOUCH Program. A CD-TOUCH version will be developed. The currently approved version for MS will be re-named as the "MS-TOUCH Prescribing Program."
Patient Discontinuation Notification Form	A form that may be used by prescribers to discontinue a patient and de-enroll them from the TOUCH Prescribing Program. A CD-TOUCH version will be developed. The currently approved version for MS will be re-named as the "MS-TOUCH Prescribing Program."
Patient Discontinuation Questionnaire	This form will be provided to prescribers when a patient discontinues TYSABRI treatment and 6 months after discontinuation. A CD-TOUCH version will be developed. The currently approved version for MS will be re-named as the "MS-TOUCH Prescribing Program."

Table 33 RiskMAP Materials (cont'd)

Material	Brief Description
TOUCH Enrollment Kit	A folder provided to potential prescribers that contains approved TOUCH Materials (listed above) and outlines specific responsibilities of each of the parties involved in the TOUCH Prescribing Program. A CD-TOUCH version will be developed. The currently approved version for MS will be re-named as the "MS-TOUCH Prescribing Program" and will contain the materials currently approved for MS, as described above.
Dear Doctor Letter	A communication containing important safety information regarding the reintroduction of TYSABRI was previously approved by the FDA and sent to neurologists. Similarly, a communication to containing important safety information regarding the approval of TYSABRI for use in CD patients will be sent to potential prescribers for CD.
Dear Patient Letter	A communication containing important safety information regarding the reintroduction of TYSABRI was previously approved by the FDA and sent to MS patients who have expressed an interest in receiving updates regarding TYSABRI. Similarly, a communication containing important safety information regarding the approval of TYSABRI for use in CD patients will be sent to CD patients who have expressed an interest in receiving updates regarding TYSABRI.
Patient Getting Started Brochure	Brochure designed to assist patients considering starting treatment with TYSABRI. Contains summary information on the known risks and potential benefits of therapy, in addition to an overview of TOUCH Requirements. A CD-TOUCH version will be developed. The currently approved version for MS will be re-named as the "MS-TOUCH Prescribing Program."
Healthcare Professional Infusion Guide	Designed for use in the infusion-setting. Provides practical step-by-step considerations for appropriate infusion of TYSABRI and reinforcement of TOUCH requirements. Currently approved materials will be used.
Tysabri.com	Website designed to disseminate approved labeling information for TYSABRI and an overview of TOUCH Program requirements.
Guidance for Evaluation of New Neurologic Symptoms in Patients Receiving TYSABRI®	Document provides guidance to healthcare professionals when undertaking the assessment and management of new or worsening neurologic symptoms in MS patients and CD patients treated with TYSABRI.
Additional Education	All gastroenterologists in the Sponsor's databases will receive periodic educational mailings. A toll-free help-line will provide prescribers and nurses access to health care professionals in Biogen Idec's medical information department who can answer questions related to TYSABRI. The Sponsor will support educational initiatives through organizations such as the Crohn's and Colitis Foundation of America (CCFA), Infusion Nurse Society (INS), International Organization for MS Nurses (IOMSN) and will facilitate Continuing Medical Education (CME) programs directed at prescribing physicians and infusion nurses.

4.2 RISK ASSESSMENT

The goals of risk assessment are:

- **To determine the incidence and risk factors for PML and other serious OI's with TYSABRI treatment.** Safety data from the TOUCH Prescribing Program will support this goal, as will data from long-term observational studies.
- **To assess further the overall safety profile of TYSABRI.** Elan and Biogen Idec will continue to study the safety profile of TYSABRI beyond 2 years of dosing and in the clinical practice setting, the nature and incidence of rare unanticipated adverse events, and the effect of TYSABRI on humoral and cell-mediated immunity. Safety data from the TOUCH Prescribing Program, the MS observational study (TYSABRI Global Observational Program in Safety - TYGRIS), the CD observational study and TYSABRI clinical trials will support this goal.

4.2.1 TOUCH Prescribing Program Safety Surveillance Goals

The TOUCH Prescribing Program is designed to assess the incidence and risk factors for PML and other serious OI's with TYSABRI treatment. In contrast to the typical post-marketing surveillance model that relies on spontaneous reporting of adverse events to the manufacturer, the Sponsor, through the TOUCH Prescribing Program, will systematically follow and actively solicit information regarding the occurrence of PML and other serious OI's through a variety of mechanisms on every TYSABRI-treated patient in the US. The TOUCH Prescribing Program will seek to provide a complete denominator of TYSABRI-treated patients (including person-years of exposure) and a complete numerator of any PML or other serious OI that may occur. In addition, careful analysis of any case of PML or other serious OI may provide insights into potential risk factors for such events.

Thus, the Sponsor will closely monitor the incidence, rate, and morbidity and mortality of PML and other serious OI over time after the re-introduction of TYSABRI into the US market. Any clinically significant change in the estimated risk of PML or other serious OI will trigger a prompt discussion with the FDA and appropriate action.

4.2.2 TYSABRI Global Observational Program in Safety in MS and CD

Elan and Biogen Idec propose that a large subset of patients in the TOUCH Prescribing Program also enroll into two voluntary observational studies called the TYSABRI Global Observational Program in Safety for CD and the TYSABRI Global Observational Program in Safety for MS (TYGRIS). Both studies have the objectives of determining the incidence and pattern of serious infections and malignancies, as well as the overall safety profile of TYSABRI, with long-term use in clinical practice.

The CD Observational Study will enroll approximately 4,000 CD patients worldwide, of which approximately 2,000 patients will be authorized in the US, and these patients will

be systematically followed for up to 5 years. Note that in the US, only prescribers and CD patients already authorized in the mandatory TOUCH Prescribing Program will be eligible to participate in the voluntary study. The objectives of this observational study are to determine the incidence and pattern of serious infections and malignancies, as well as the overall safety profile of TYSABRI in CD patients with long-term use in clinical practice. The smaller sample size of the CD observational study compared with the MS observational study is appropriate due to the potentially higher rate of serious opportunistic infections in CD patients based on event rates observed within placebo-controlled and open-label studies of TYSABRI for CD.

TYGRIS enrollment has been initiated. TYGRIS will enroll approximately 5,000 MS patients worldwide, of which approximately 3,000 patients will be enrolled in the US, and these MS patients will be systematically followed for up to 5 years. An update on the progress of TYGRIS is provided in Section 4.3.1.1.

Whereas the TOUCH Prescribing Program is focused on determining the incidence of PML and other serious OI's, the CD and MS Observational Studies will evaluate newly emerging risks, if any, with TYSABRI monotherapy treatment in CD and MS patients. While the safety profile of TYSABRI in clinical trials has been well-characterized regarding the incidence and nature of common serious adverse events over a 2-year period, the incidence of rare events, the safety profile beyond 2 years, and the safety profile in clinical practice will be better characterized in this study.

Prescribers participating in the observational studies are instructed to report any serious adverse event to Biogen Idec within 24 hours of the site becoming aware of the event. Participating prescribers will also be contacted every 6 months and will be asked to provide any serious adverse events that they have not yet reported as well as the patients' exposure to any concomitant antineoplastic, immunomodulatory or immunosuppressant therapies, or systemic corticosteriods.

In the TYGRIS study, a sample size of 5000 MS patients will be enrolled and followed for 5 years whether continuing on TYSABRI or not. There will be approximately 18,700 patient-years of TYSABRI exposure and 5300 patient-years of off-treatment follow-up. This study design will allow the detection of important rare serious adverse reactions that occur with an incidence of 0.05% with 92% probability and 0.10% with over 99% probability.

In the CD Observational Study, a sample size of 4000 CD patients will be enrolled and followed for 5 years whether continuing on TYSABRI or not, generating approximately 13,400 patient-years of TYSABRI exposure and 5,600 patient-years of off-treatment follow-up in this study. This study design will allow the detection of important rare serious adverse reactions that occur with an incidence of 0.06% with a 91% probability and an incidence of 0.10% with 98% probability.

4.2.3 Pregnancy Registry

A Pregnancy Registry has been established in the US to determine the safety of TYSABRI in pregnant patients. Approximately 300 TYSABRI-exposed pregnant MS patients will be authorized. CD patients will also be enrolled in this pregnancy registry.

4.2.4 Additional Studies

Re-Dosing - In order to evaluate the safety of TYSABRI with re-exposure after an interval without treatment, Biogen Idec is conducting two multi-national, open-label re-dosing studies. Up to 1,500 patients with MS who previously received TYSABRI treatment during their participation in clinical studies will be enrolled. A similar study in CD is planned.

Plasma Exchange - Study 101-MS-001 "A Multicenter Study to Assess the Effect of Plasma Exchange in Accelerating the Clearance of Natalizumab in Patients with Multiple Sclerosis" was initiated in December 2006, to determine if plasma exchange increases the clearance of natalizumab from systemic circulation. The study will determine if plasma exchange has potential as a therapeutic intervention in the event of suspected or confirmed progressive multifocal leukoencephalopathy (PML), given the importance of immune reconstitution as a treatment for this disease.

4.2.5 Effect of TYSABRI on Immune Function

Biogen Idec is proposing to conduct a study of approximately 100 MS patients to further evaluate the effect of TYSABRI on humoral and cellular immunity to recall and neo-antigens. Data from this study may provide information into potential immunological risk factors for PML with TYSABRI treatment.

4.3 EVALUATION/QUALITY PLAN

Elan and Biogen Idec are committed to evaluating the effectiveness of the TYSABRI RiskMAP and reporting the results on a quarterly basis to the FDA. Each submission will include two major datasets: (1) Health Outcomes Data (e.g., PML rate, overall safety), and (2) Systems/Process Data, Quality and Compliance Metrics (e.g., distribution system details, health care professional knowledge of TYSABRI use instructions).

A key feature of the Sponsor's RiskMAP evaluation process is internal senior management review of these data by a multi-disciplinary TYSABRI Risk Management Review Committee.

The Evaluation/Quality Plan will allow Elan and Biogen Idec to assess the effectiveness of the RiskMAP in an ongoing fashion and to improve the plan, as necessary.

Information on drug safety will be provided as part of the periodic safety update report (PSUR) every 3 months for first 2 years, then semi-annually. Other information related

to the conduct of the Risk MAP will be provided quarterly for the first year, biannually (every 6 months) for 2 years, then annually thereafter.

4.3.1 Update on TYGRIS Implementation and MS-TOUCH Program

4.3.1.1 Update on TYGRIS Implementation

The TYGRIS study (TYSABRI® Global Observational Program in Safety) is an observational cohort study designed to obtain long-term safety data on patients with multiple sclerosis (MS) treated with TYSABRI® in a clinical practice setting. It is anticipated that approximately 3,000 patients from the US will be enrolled in Protocol # 101-MS-402 and 2,000 patients will be enrolled from the rest of the world in Protocol # 101-MS-403. Protocol # 101-MS- 403 began enrolling patients in the EU in September 2006. Protocol # 101-MS-402 began enrolling patients in the US in January 2007.

As of May 23, 2007, 350 patients have enrolled in TYGRIS: 261 patients from Germany, 19 from Austria, and 31 from The Netherlands, 2 each from Ireland and Denmark, and 35 from the United States. The median age of TYGRIS patients was 39 years; the majority of patients (67%) were women; 92% had received prior immunomodulatory or immunosuppressant treatment. The median duration of MS symptoms in enrolled patients was 9 years.

Of the 350 patients enrolled in TYGRIS, 299 patients have started TYSABRI treatment. There has been only one report of serious infection, sepsis secondary to pneumonia. There have been no reports of confirmed PML or other serious opportunistic infections or malignancies.

4.3.1.2 Update on MS-TOUCH Prescribing Program

The MS TOUCH Prescribing Program has been successfully implemented with the re-introduction of TYSABRI in June 2006. The information presented in this section is through the data cut-off date of 23 May 2007.

Approximately 11,000 patients have been enrolled in the TOUCH Prescribing Program in the US, of which 8,313 patients have been treated with TYSABRI. Within the TOUCH Prescribing program, the median number of TYSABRI infusions administered to each patient was four. 97.4% of patients have been previously treated with an MS therapy. Approximately 1,750 physicians have enrolled patients into the program and 1,750 infusion sites have been trained and authorized.

Program compliance is excellent, based on several metrics encompassing patient and prescriber enrollment, controlled distribution of drug shipments, as well as the Sponsors' receipt of Patient Status Report and Reauthorization Questionnaires and Pre-Infusion Patient Checklists. 99.9% of natalizumab infusions were administered to patients enrolled in the program. Since enrollment into the program involves reading and signing the Prescriber/Patient Acknowledgement, this indicates that patients and prescribers are

making informed benefit-risk decisions regarding TYSABRI before the start of therapy. 96.8% of patients have received no immunomodulatory or immunosuppressant therapies concurrently with natalizumab. Thus, natalizumab is being prescribed predominantly as a monotherapy, as indicated in the current labeling for MS. The Sponsors sent 10,125 shipments of TYSABRI, of which 99.9% of these shipments were delivered to authorized infusion sites. 2740 re-authorization forms were expected, of which 99.6% were received. 99.9% of the 38,898 infusions administered had a completed Pre-Infusion Patient Checklist. The physician was successfully contacted by the infusion center for 98.4% of the 3,123 Pre-Infusion Patient Checklists that required a physician authorization. Thus, the TOUCH Prescribing Program is encouraging clinical vigilance regarding new or worsening neurological symptoms, facilitating use of TYSABRI as a monotherapy and not treating patients who are immunocompromised.

Biogen Idec fielded a knowledge and behavior survey to understand prescribers and infusion site nurses' knowledge of the key risk management messages of the TYSABRI Risk Management Program and the actions taken to minimize risk. The respondents were recruited from lists prepared by Biogen Idec of neurologists and infusion sites who had enrolled in the TOUCH Prescribing Program. The lists contained 1,275 Neurologists and 1,406 Infusion Sites. Of those, all were contacted via email (when available), fax and telephone. From this, 184 infusion site nurses and 135 neurologists agreed to participate. One hundred three neurologists (8%) and 139 (10%) of the infusion site nurses completed the survey. Overall, prescribers and nurses understood the risk of PML and other serious OIs with TYSABRI treatment and the indicated population. 99% of prescribers and 89% of infusion nurses understood that TYSABRI increases the risk of PML. 98% of physicians and 96% of infusion nurses correctly identified the indication for TYSABRI. At least 92% of prescribers and 94% of infusion nurses understood the key program requirements. Thus, surveys of enrolled prescribers and infusion nurses indicate high levels of PML awareness and understanding of the RiskMAP requirements.

Cumulative data from the TOUCH Prescribing Program suggest a similar safety profile to those seen in previous clinical studies of TYSABRI. As of May 23, 2007, there have been no new reports of confirmed cases of PML or OI's, although the long-term safety data are limited. Thus, the TOUCH Prescribing Program has been successfully implemented for the MS indication and the data continue to support the favorable benefit-risk profile of TYSABRI for patients with relapsing forms of MS.

4.4 CONCLUSION

Elan and Biogen Idec have developed a comprehensive risk management plan that encompasses both risk minimization and risk assessment. The plan is designed to promote informed benefit-risk decisions between physicians and patients regarding the use of TYSABRI, to minimize morbidity and mortality due to PML through early detection with clinical vigilance, and to minimize the risk of PML by treating only non-immunocompromised patients and strongly discouraging concurrent use with immunosuppressants or immunomodulators.

The risk management plan was designed specifically to take advantage of the unique aspects about the medical management of patients with CD and MS. The program includes enrollment of prescribers and patients and a controlled, centralized distribution of TYSABRI only to authorized infusion centers that Elan and Biogen Idec have trained on PML risk and appropriate use of TYSABRI. Through the use of multiple tools, the program facilitates the education of physicians, infusion nurses, and patients about the appropriate use of TYSABRI, the risk of PML, and the importance of early detection of PML through clinical vigilance. In addition, Elan and Biogen Idec also plan several clinical studies to determine the incidence of, and risk factors for, PML with TYSABRI treatment and to further assess the overall safety profile of TYSABRI.

The TYSABRI risk management plan strikes a balance between the need to minimize the risk of a rare, but serious, adverse event and provide TYSABRI's significant benefit to appropriate patients with CD or MS, without placing unnecessary burden on physicians, infusion nurses, and patients. Finally, Elan and Biogen Idec will continually assess the risk management plan and the information that it generates and, as needed, make modifications to improve its effectiveness.

5 BENEFIT-RISK CONSIDERATIONS

Crohn's disease is a lifelong, chronic, disabling disease that can begin at any age, but has a peak incidence in young adults. Patients experience significant decrease in their HRQoL from their disease and treatment-related complications. Importantly, mortality from this disease is increased relative to the general population. A step-wise approach is utilized for the treatment of CD, but patients continue to fail all currently available conventional therapy. New agents are needed to meet the needs of Crohn's patients who continue to have disease activity despite therapy, including those who have exhausted all available medical treatment options. In the absence of a cure, the objective of treatment should be to provide patients with prolonged periods of corticosteroid-free remission, improved quality of life, and a low prevalence of side effects.

Natalizumab meets many of these needs:

- The natalizumab clinical development program has demonstrated induction efficacy in patients with moderate to severely active CD with objective evidence of active inflammation as demonstrated in Study C307 and the corresponding sub-group in Study CD301. The onset of effect is within 4 weeks.

- Study CD303 provides evidence for clinical benefit of natalizumab as maintenance treatment. More than twice the proportion of natalizumab-treated patients maintained response or remission at each study visit for an additional 12 months compared to those re-randomized to placebo treatment. The sustained maintenance efficacy observed with natalizumab treatment addresses an important aspect of the unmet need in CD: prolonged maintenance of remission and response.
- Nearly 40% of patients enrolled in the induction studies were taking steroids but still had active disease. Natalizumab ameliorated signs and symptoms of disease but also permitted many to discontinue the use of steroids and, thereby, reduce the known significant risks associated with chronic steroid treatment. Clinicians uniformly want to reduce the use of steroids but often cannot because of disease flares associated with the attempted tapering of steroids. In view of the safety issues associated with chronic steroid treatment, the effect of natalizumab in reducing the need for steroids is an important benefit.
- Approximately 25% of patients enrolled in the CD clinical trials had previously been treated with inhibitors of TNF-α, discontinuing primarily due to lack of efficacy or intolerance to therapy. In *post-hoc* analyses, natalizumab was shown to be at least as efficacious in such patients as in the overall population with no apparent differences in safety profile.
- CD patients enrolled in the natalizumab program were found to have a significantly lower HRQoL, compared to the general population in North America. An improvement in HRQoL was seen with treatment in CD301 and this improvement

was sustained with natalizumab treatment during CD303 in a significantly greater proportion than the group re-randomized to placebo. Notably, at the completion of CD303, the mean scores of those receiving natalizumab were found to be comparable to the general population on both the Physical and Mental Component Summaries of the SF-36.

Although many therapies for CD are initially effective, over time their efficacy is lost, and patients experience increasing symptoms. Two monoclonal antibodies to TNF-α, infliximab and adalimumab, are currently the only biological therapies approved to treat patients who have moderately to severely active CD, and who have not responded despite therapy with a corticosteroid and/or an immunosuppressant. However, these inhibitors of TNF-α have several principal limitations:

- Lack of, or loss of response/remission: Approximately 40% of patients will not respond to their initial induction regimen with infliximab, and of those patients who do respond and continue therapy, more than 60% will fail to maintain clinical remission after a year of therapy (Hanauer 2002). Only approximately 25% of patients in whom infliximab therapy is initiated are in remission after one year without the use of concomitant corticosteroids (Remicade Prescribing Information).
- Antibody development: 10-61% of patients treated with infliximab develop antibodies (Remicade Prescribing Information). As a result, oral immunosuppressants are often required as concomitant treatment to reduce the development of antibodies, or dose escalation is utilized in an attempt to restore efficacy.
- TNF-α inhibitors are potent modulators of immune function and can be associated with serious adverse events, particularly OI's and malignancies (primarily lymphomas). Other potential adverse events include sepsis and pneumonia, severe hepatotoxicity, exacerbation of heart failure, hematologic events, hypersensitivity reactions, demyelinating disorders, and lupus-like syndrome.

To date, the aforementioned serious adverse events associated with other immunomodulatory agents have been managed by educating prescribers and patients about the potential risks, as well as investigating the risk with continued exposure. The efficacy of these products and the disabling nature of the diseases they treat necessitate that physicians and patients carefully consider the benefits and risks of treatment prior to treatment initiation. Physicians and patients, utilizing this information, must decide whether these treatments are the correct therapeutic options for them.

Natalizumab is an immunomodulatory agent that offers the potential of great benefit to patients with CD unresponsive to conventional therapy and in need of a biological therapy. In addition, natalizumab provides sustained efficacy in the absence of concomitant immunosuppressive medication use, providing a choice of therapy to physicians faced with patients unresponsive to conventional therapy. Like other highly

active drugs used to treat autoimmune diseases, it is not without risk. The most important risks of natalizumab treatment are hypersensitivity reactions and OI's, including PML.

- Hypersensitivity reactions occurred in approximately 3.5% of patients with serious systemic reactions being reported in 0.1% of patients. These hypersensitivity reactions are most frequently seen in patients who develop antibodies to natalizumab. Taken together with the fact that efficacy is reduced in patients with antibodies, the sponsors recommend discontinuing treatment with natalizumab in those who develop persistent antibodies.
- The incidence of malignancy is increased in natalizumab-treated patients compared with placebo-treated patients in the short-term placebo-controlled CD studies. However, the time period for this assessment is short (≤16 weeks) and the confidence intervals are wide making an association with drug unlikely. In the longer-term MS placebo-controlled trials and in the pooled CD and MS experience, the incidence of malignancy is similar for natalizumab- and placebo-treated patients. It is recognized that malignancy signals may take years to evaluate adequately; thus the long-term incidence of malignancy in natalizumab-treated patients will be further evaluated in the CD observational study.
- In natalizumab-treated patients, there have been isolated cases of serious infection with opportunistic agents, including PCP, pulmonary aspergillosis, and others. In some of these patients, concomitant factors such as coexisting medical conditions or concomitant therapies for CD may have played a role in the infections. The most common OI with natalizumab has been PML (3 cases). After a comprehensive re-assessment of MS and CD natalizumab patients, the incidence of PML is estimated at approximately 1/1,000 (95% CI 0.2 to 2.8/1,000; Yousry *et al* 2006). The three patients who developed PML were either receiving concomitant treatment with an immunomodulator or were immunocompromised from prior immunomodulator use. PML generally occurs only in patients with altered immune function. To reduce the level of this risk, the proposed labeling warns against the use of natalizumab in immunosuppressed patients or concomitantly with chronic immunosuppressant or other immunomodulatory therapies.
- From time of re-launch in June 2006 until May 23, 2007, approximately 11,500 patients have received natalizumab in the post-marketing setting worldwide and there have been no new confirmed cases of PML or serious OI's reported.
- Natalizumab was generally well-tolerated by patients for periods of up to 2 years. Common adverse events were comparable to placebo and the incidence of infections, including serious infections, were similar to patients treated with placebo.

Physicians and patients should have the opportunity to decide if natalizumab is right for them. The Sponsor has received feedback from many gastroenterologists and CD

patients that they want access to an effective treatment for CD unresponsive to conventional therapy and are willing to have these discussions and make choices regarding the risks. A recent survey of CD patients indicated that patients have well-defined preferences among treatment attributes and are willing to accept risks in exchange for efficacy. In the study of 580 CD patients in the US, both with and without prior natalizumab exposure, 90% of patients would accept the currently observed risk of PML death or disability with natalizumab to obtain a clinically relevant benefit of the type demonstrated with natalizumab (Sands *et al* 2006).

The Sponsor accepts the responsibility to ensure that patients and prescribers are fully informed of all current knowledge regarding appropriate use conditions for natalizumab. Accordingly, a comprehensive risk management plan (Section 4) that encompasses both risk minimization and risk assessment has been proposed.

- The program is based upon product labeling that would:
    - Clearly limit its use to appropriate CD patients who have failed conventional therapy,
    - Warn against use in combination with other immunosuppressant therapy, and
    - Describe the risks of natalizumab treatment.
- Through the use of multiple tools, the risk management program facilitates the education of healthcare providers and patients about the appropriate use of natalizumab, the risk of PML, and the importance of early detection of PML through clinical vigilance.
- An important consideration regarding benefit-risk in CD will be duration of therapy. Initiation of therapy in CD occurs due to flares of disease activity and response to therapy is generally rapid and readily apparent. In the case of natalizumab, if therapy is not effective, clinicians will discontinue use of the drug such that any long-term risks of therapy will be borne only by those who benefit.
- In addition, as with the TOUCH program that has been in place for the MS indication since July of 2006, the CD program includes:
    - Mandatory enrollment of all prescribers and patients into the TOUCH Prescribing Program (a registry that provides diligent safety surveillance and systematic tracking of all patients),
    - Mandatory training and enrollment of all infusion sites (and all central pharmacies affiliated with authorized infusion sites) into the TOUCH Prescribing Program,

  - A controlled distribution system for natalizumab so that natalizumab is delivered to and administered only to authorized infusion sites,
  - Mandatory completion of the Pre-Infusion Patient Checklist and distribution of the Medication Guide to each patient prior to each monthly TYSABRI dose,
  - Real-time submission of Pre-Infusion Patient Checklists to monitor infusion site compliance and to track TYSABRI dosing on a patient-specific basis,
  - Mandatory prescriber reauthorization of natalizumab dosing for each patient every 6 months,
  - An integrated, computerized validated database that captures enrollment, patient tracking, and drug distribution data.

- Safety data from the TOUCH Prescribing Program will assist in determining the incidence and risk factors for PML and other serious OI's with natalizumab treatment. The Sponsor also proposes that a large subset of patients in the TOUCH Prescribing Program enroll into a voluntary observational study to determine the incidence and pattern of serious infections and malignancies, as well as the overall safety profile of natalizumab with long-term use in clinical practice.

In summary, natalizumab is a highly effective treatment for inducing and maintaining clinical benefit in CD patients who have failed conventional therapy. These patients require treatment with a biological therapy, and natalizumab provides another treatment choice for physicians and patients. The degree of efficacy and overall safety profile demonstrated in the clinical studies, combined with the ability to minimize the risk for PML with the proposed label and risk management plan, lead to a benefit/risk ratio that is acceptable and will allow physicians and patients to consider natalizumab as a valuable treatment option for CD.

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