28 April 2016
EMA/458317/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zinbryta

International non-proprietary name: daclizumab

Procedure No. EMEA/H/C/003862/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AI	Autoinjector
ADA	Anti-Drug Antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AED	Antiepileptic Drug Use
BPF	Brain Parenchymal Fraction
CBC	Complete Blood Counts
CDA	Clinical Disease Activity
CD	cluster of differentiation
CDC	complement dependent cytotoxicity
CDP	Confirmed Disability Progression
CSR	Clinical Study Report
DAC	Daclizumab
DAC HYP	Daclizumab High Yield Process
DDI	Drug-Drug Interaction
DIS	Dissemination In Space
DIT	Dissemination In Time
DMT	Disease modifying Therapy
ECL	electrochemiluminescence
ELISA	enzyme linked immunosorbent assay
FAS	Full Analysis Set
FS	Functional Score
Gd	Gadolinium
GD-CEL	Gadolinium Contrast Enhancing Lesion
GLP	Good Laboratory practice
HLT	High Level Term
HV	Healthy Volunteer
IAR	infusion-associated reactions
IL	Interleukin
INEC	Independent Neurology Evaluation Committee

ISS	Integrated summary of safety
mAb	monoclonal Antibody
MeDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
N/A	Not Applicable
NAb	Neutralising antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PPMS	Primary Progressive Multiple Sclerosis
QoL	Quality of Life
PFP	PreFilled Pen
PFS	PreFilled Syringe
PIP	Pediatric Investigation Plan
RAP	Relapse Adjudication Panel
RMP	Risk Management Plan
RMS	Relapsing Remitting Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAD	Sustained Accumulation of Disability
SC	Subcutaneous
SCS	Summary of Clinical Safety
SF-12	SF-12^{R} Health survey
SRD	Sustained Reduction in Disability (reverse of SAD)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 6 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zinbryta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Zinbryta is indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The applicant indicated that daclizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0147/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0147/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance daclizumab contained in the above medicinal product to be considered as a new active substance in comparison to the known daclizumab previously authorised in the European Union as Zenapax and claimed that daclizumab (Zinbryta) is a biological substance previously authorised as a medicinal product in the European Union, but differing from the known daclizumab previously authorised in the EU as Zenapax in molecular structure, nature of the source material or manufacturing process.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes

- The application was received by the EMA on 6 March 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2015.
- PRAC assessment overview, adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2015.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

  A GCP inspection was conducted in Serbia and Russia at 2 investigator sites between August and September 2015. The integrated inspection report of the inspection carried out was issued on 2nd November 2015. At the inspection of Clinical Center of Vojvodina (Inspection Site 1 - Serbia) there were no critical, 5 major and 12 minor findings. The major findings were related to the Research Ethics Committee, clinical conduct of the trial, data management and source data. At the inspection of Clinic Medinef (Inspection Site 2 - Russia) there were no critical, 2 major and 14 minor findings. The major findings were related to clinical conduct of the trial and source data. The conclusion of the report states that “it appears that the data in the CSR are sufficiently reliable for assessment for the marketing authorisation with no issues noted from these two sites that would cast serious doubt on their reliability.”
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 26 November 2015.
- PRAC assessment overview, adopted by PRAC on 3 December 2015.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of

Outstanding Issues to all CHMP members on 5 February 2016.

- PRAC assessment overview, adopted by PRAC on 11 February 2016.
- During the CHMP meeting on 30 March 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zinbryta.

2. Scientific discussion

2.1. Executive summary

Multiple sclerosis is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and neuronal loss.
The pathological changes underlying MS are believed to be mediated by activated, autoreactive lymphocytes which cross the blood-brain barrier (BBB) and initiate an immune-mediated cascade of events that injures both the grey and white matter of the brain [Frohman 2006]. MS affects approximately 2.5 million people worldwide and is the most common cause of neurological disability among young adults. It is usually diagnosed between the ages of 20 to 40 years, with twice as many women affected as men.

Relapsing MS (RMS) is the most common clinical presentation of the disease. The diagnosis of RMS is usually made on the basis of both clinical and radiographic criteria and it requires that a patient experience at least 2 neurologic events, consistent with demyelination separated both in time and in location in the CNS. Patients with RMS experience discrete episodes of neurological dysfunction (referred to as relapses, exacerbations, or attacks), each lasting several days to several weeks, that occur intermittently over many years. Typical symptoms of relapse include weakness, sensory loss, visual loss, and imbalance.

Early in the course of the disease (the relapsing-remitting MS [RRMS] phase), the physical symptoms of relapse tend to subside completely after each attack. However, the CNS inflammatory process that accompanies the clinical relapses during the RRMS phase results in lasting brain injury as detected by early grey-matter atrophy and increased lesion load on magnetic resonance imaging (MRI) that predispose individuals to long-term disability [Dalton 2004; Fisniku 2008]. Over time, the clinical recovery from relapses tends to be incomplete, leading to the accumulation of functional disability and the frequent onset of secondary progressive MS.

The prevention of clinical relapses and disability progression as well as the subclinical brain injuries that occur during the relapsing phase of MS are recognized as important therapeutic benefits for MS patients. Clinical relapses impair essential activities of daily life and frequently result in hospitalization. An estimated 42% to 57% of relapses are associated with residual neurological deficits [Hirst 2008; Lublin 2003]. The goal of relapse prevention applies to patients with both relapsing-remitting MS and other forms of relapsing MS (such as secondary relapsing MS), and recent consensus panels on the treatment and classification of MS have underscored the importance of inflammatory activity (as defined by the presence of clinical relapses and new MRI lesions) in both relapsing and progressive forms of MS as an indication for disease-modifying treatment [Costello 2014; Lublin 2014]. Without effective treatment, approximately half of all RMS patients are unable to walk without assistance within 15 years of their diagnosis, and more than half may eventually die from disease-related complications.

MS pathology in the cerebral white matter is characterized by focal areas of demyelination and axonal injury and, in acute lesions, by activated T-lymphocytes in the adjacent perivascular spaces and migration of inflammatory cells through a compromised BBB. Autoreactive T-cells directed against myelin antigens in the CNS play a role in the initiation and propagation of MS lesions, contributing to the destruction of myelin, axons, and oligodendrocytes through both direct and indirect effects of inflammation.

MS pathology in the cerebral grey matter is now recognized to be an important contributor to disability progression in MS. MS grey matter or cortical pathology has distinct characteristics from white matter pathology because it is generally devoid of parenchymal lymphocytes and is closely associated with the presence of ectopic lymphoid tissue in the meningeal and subpial regions. Cortical injury can occur independently of white matter pathology where it may contribute to disability progression independently of clinical relapses or focal lesions on brain MRI.

Daclizumab works through a novel, reversible modulation of IL-2 signalling, inhibiting CD25- dependent, high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact [Martin 2010]. This signalling modulation results in several well-characterized immunologic changes that were hypothesized to result in selective targeting of both white and grey matter MS pathology while also preserving key protective functions of the immune system, as follows:

- Since activated but not resting T-cells express CD25 and depend on the high-affinity receptor to respond efficiently to IL-2, daclizumab selectively inhibits activated T-cells without causing a nonspecific immunodepletion of lymphocytes.
- Daclizumab (Zinbryta) treatment results in an expansion of immunoregulatory NK cells, the CD56bright natural killer (NK) cell. CD56bright NK cells have been shown to selectively target activated but not resting T-cells in MS, and the magnitude of their expansion post-treatment has correlated with the therapeutic response to daclizumab.
- Regula tory T-cells (Tregs) express CD25 and play an important role in immune system homeostasis and regulation. While there is a reversible decrease in the number of circulating Tregs during Zinbryta treatment, Tregs express high levels of the intermediate affinity IL-2 receptor, thereby enabling continued response to IL-2 signals. The cellular proliferation status, cytokine production profile, and epigenetic markers of the FOXP3 promoter indicate that a stable and functionally competent population of Tregs is maintained in the presence of long-term daclizumab treatment despite CD25 antagonism. Compared to previously authorised daclizumab (Zenapax), daclizumab (Zinbryta) has a decreased amount of antibody-dependent cellular cytotoxicity in vitro, and this was considered to be advantageous for maintaining Treg cell populations during long-term use.

In summary, the novel IL-2 signalling modulation of daclizumab (Zinbryta) represents a targeted and reversible therapeutic approach to MS treatment that can selectively impact both grey and white matter MS pathology without causing nonspecific immunodepletion. Daclizumab's mechanism of action is distinct and differentiated from other therapies available to treat RMS. The impact of daclizumab (Zinbryta) on Tregs has been an area of potential concern but the demonstration of functional adaptation by Tregs during Zinbryta use as well as the expansion of other immunoregulatory cell populations provided a basis for managing any potential impact on Tregs. Therefore, daclizumab (Zinbryta) was systematically evaluated in clinical studies to define its risks and benefits in relapsing MS.

Current Treatments for Multiple Sclerosis and Unmet Need

Therapies for MS include symptomatic treatments (e.g., steroids) and disease-modifying therapies (DMTs). The available therapies entail difficult trade-offs between efficacy, safety, tolerability, and convenience that make RMS a challenging condition to treat successfully, and that result in substantial need to provide new options that can improve these balances for some patients.

Commonly used RMS and RRMS therapies include the interferon-beta (IFN β) therapies and glatiramer acetate (GA) that, depending upon the agent, require either intramuscular (IM) or subcutaneous (SC) injections, from as few as every 2 weeks to as many as 7 times a week. While these treatments have

well-established safety and efficacy profiles, many subjects continue to experience significant MS disease activity while on treatment. Furthermore, these therapies are associated with known side effects, such as flu-like symptoms for the IFN-β therapies, and lipoatrophy and other injection site pathologies for GA, which can be a significant burden for some patients. Available data suggest that approximately 40% of MS patients may not adhere to prescribed injectable therapies for MS out of fear of, or the inconvenience associated with, such frequent injections.

Dimethyl fumarate, fingolimod, and teriflunomide are oral DMTs that are approved for the treatment of RRMS. While these therapies offer an improved route of administration for some patients, they nonetheless require daily administration and furthermore some patients may not tolerate them or continue to experience disease activity while on treatment. Oral therapies have also been associated with clinically important side effects, such as lymphopenia for dimethyl fumarate; bradycardia, atrioventricular block, and macular oedema for fingolimod; and hepatotoxicity and lymphopenia for teriflunomide. These risks may necessitate exclusion of vulnerable patients and require specialized monitoring both during and prior to initiation of therapy.

Other available DMTs include natalizumab, which, although highly effective, is associated with the risk of progressive multifocal leukoencephalopathy (PML). Therefore, in some regions, natalizumab is authorized as a second-line therapy in patients with highly active disease and as a first-line therapy in patients with rapidly evolving severe disease.

Alemtuzumab is a monoclonal antibody that has shown superior efficacy to IFN β-1a but that entails risks of life-threatening autoimmune disorders, including fatal thrombocytopenia and nephropathies; additionally, autoimmune thyroid disease is common during treatment. For these reasons, in some regions its use is restricted to those patients who have failed other therapies or is not approved for patients with inactive disease.

Mitoxantrone is another therapy that is also associated with significant risks, including cardiotoxicity, which increases with cumulative dose; therefore, mitoxantrone is mainly used as a third-line therapy in patients with severe MS who have already failed other therapies. In summary, while several DMTs are currently available, MS patients face difficult trade-offs between benefits and risks when selecting a therapy. These risks include inadequate disease control, life-threatening adverse events (AEs), need for frequent injections or daily oral therapy, and/or tolerability problems that reduce treatment adherence and quality of life. Given the heterogeneity of MS and of patients' response to therapy, disease control is frequently incomplete after initiation of treatment, and patients must often switch from one treatment to another as their disease progresses, or their response to a given treatment proves to be unsatisfactory based on safety, efficacy, or tolerability.

Therefore, there remains an unmet medical need for new, alternative high-efficacy treatment options that have demonstrated superior efficacy to current standards of MS care, that offer advantages in terms of frequency of administration, and that have manageable risks. Daclizumab, the active substance in Zinbryta,was developed to address this unmet need.

2.2. Quality aspects

2.2.1. Introduction

Daclizumab is a humanized monoclonal antibody (mAb) that binds to CD25, the alpha subunit of the human high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling.

The final product, Zinbryta, is presented in a pre-filled syringe or pre-filled pen with a nominal amount of 150 mg per dose for subcutaneous administration.

2.2.2. Active Substance

General information

The active substance is a recombinant humanized IgG1 monoclonal antibody expressed in a NS0 cell line, purified to a high degree of purity. Daclizumab binds to the alpha subunit (CD25) of the human high-affinity interleukin-2 (IL-2) receptor, which is expressed on the surface of activated lymphocytes. The isotype of daclizumab is IgG1κ.

Daclizumab is glycosylated at amino acid 296 of both heavy chain subunits with the major oligosaccharide form existing as a core fucosylated biantennary structure. The N-terminus of the daclizumab heavy chain exists as three major forms of charge variants. The C-terminus of the heavy chain exists with and without the C-terminal lysine residue. The major form lacks the C-terminal lysine residue, resulting in a C-terminal glycine.

Manufacture, characterisation and process controls

Daclizumab is expressed in NS0 cells (a mouse myeloma cell line) using recombinant DNA technology. The cell culture process is conventional, expanding the culture via shake flasks and progressively larger bioreactors to inoculate a production bioreactor. The purification steps include harvest, several chromatography and viral inactivation/filtration steps, and ultra/diafiltration, before dispensing into containers for storage at 2-8°C.

Manufacturing flow charts identifying the various controlled parameters and in-process controls/tests for each step were presented.

A comprehensive batch numbering system identifies the stage of manufacture, the year and the consecutive numbering of batches of that active substance for the year.

Cell banking system, characterisation, and testing

Daclizumab is produced by expression in NS0 cells that have been stably transfected with a single expression vector, expressing both the daclizumab humanized light and heavy chain genes encoding the region that binds to the alpha subunit (CD25) of the IL-2 receptor.

A two-tiered cell banking system using master cell banks (MCB) and working cell banks (WCB) is in place. The source, history and production of the NS0 cells, MCB and WCB have been described and documented in detail, including methods and reagents used during culture, *in-vitro* cell age studies, and storage conditions according to ICHQ5B. Both MCB and WCB have been qualified and characterised by extensive testing for mycoplasma, sterility and adventitious viruses to establish purity.

Cell culture

Detailed descriptions of the fermentation and harvest process have been provided and include the identification of controlled parameters as well as acceptance criteria.

Sequential time lapses are identified and minimal hold times, from expansion to production bioreactor harvest, are of no concern.

Throughout each stage of the inoculum expansion step, from the flask to the bioreactor expansion phases as well as for the production bioreactor phase, the target cell density is defined and the culture medium volume adjusted. Cell density and culture time are defined for all the culture steps. Clarification was provided on the calculation of the cumulative cell growth present in the cell culture mass used in the production bioreactor phase. Limits on cumulative cell age are defined and remain below the *in vitro* cell age as qualified during process development.

Purification and formulation

Each manufacturing step of the purification process has been described along with detailed descriptions of the processing conditions and in process controls.

The purification process consists of multiple chromatography steps. Column integrity is checked prior to application of the next batch. Resin reuse is defined for each chromatography column based on both prospective scaled-down development studies and manufacturing scale data.

In addition, viral inactivation/filtration steps are performed.

The active substance is then concentrated by ultrafiltration/diafiltration prior to filtration and dispensing into containers for storage.

Purification is sufficiently described. For all column resins reuse conditions are defined. The hold times were defined at each step based on scaled-down hold time studies on various process intermediates to assess both microbial and biochemical stability. Maximum hold times were set supported by these studies.

The manufacturing process is sufficiently described and controlled parameters along with in-process tests and in-process controls are described for each of the steps in process description.

The final bulk preparation obtained after a final filtration includes a possible re-processing step consisting of a final re-filtration. It was adequately demonstrated that there was no impact on the quality of the active substance.

The active substance is stored in single use flexible containers for which compliance has been demonstrated.

Control of Materials

Selection of the clone, sub-cloning strategy and generation of the seed bank is sufficiently described. The seed bank was found to be negative for mycoplasma, bacterial, and fungal contamination and was genetically characterized before being used to prepare the MCB and WCB. Sequencing data matched the known reference sequences.

The qualification program of the cell banks is generally in agreement with ICH requirements. Identity of the cell banks was confirmed to be of murine origin. Safety studies included the tests for sterility, mycoplasma and adventitious viruses, as expected for a cell line of murine origin. Genetic stability was confirmed in MCB and extended end-of-production cell bank (EEPCB) cells used to determine the limit of *in vitro* cell age.

Safety testing to demonstrate absence of adventitious agents in the cell banks was performed on the MCB, WCB lots and on the EEPCB derived from those WCB. Bovine and porcine viruses were tested on MCB and EEPCB. This is acceptable as no animal-derived materials are introduced in the manufacturing process. Viral safety testing is also performed for the unprocessed bulk harvest.

An adequate control of adventitious agents is performed on cells banks. During early development of the cell line, foetal bovine serum (FBS) was used in the cell culture medium. However, no material of animal or human origin is used in the entire commercial manufacturing process. The Certificate of Analysis and the EDQM Certificate of Suitability for the FBS used during preparation of the seed bank were provided.

Certificates of Analyses (CoAs) for all raw materials were provided.

The information provided on raw materials listed as non-compendial and compendial is sufficient. Adequate microbial control of these materials is ensured prior to use in the manufacturing process.

Control of critical steps and intermediates

All the process input and output parameters tested were presented. The rationale is based on previous process knowledge and development and validation studies.

Microbial controls are implemented at various process steps with set limits.

Neither product-related impurities nor process-related impurities are tested as in process controls. The omission of testing for the process-related impurities was accepted based on the outcome of the impurity clearance validation performed (see process validation). Validation of the manufacturing process ensures that host cell proteins, host cell DNA and other process-related impurities are cleared to safe levels. Viral safety is assured by in process testing and viral clearance studies.

Process validation and/or evaluation

Process consistency validation was performed and the results of both the input and the output parameters of each process step for the batches assessed were provided. These batches are considered to have satisfactorily qualified the production bioreactors. The results provide assurance that the cell culture, harvest, purification, formulation, and filtration steps of the active substance manufacturing process are under control and perform consistently within the pre-defined action limits and specifications.

Process-related impurities clearance validation was performed. Impurity clearance validation with multiple batches provided the basis for omitting the testing as in process controls or to be included in active substance specifications. As those methods are not part of the specifications information on method qualification was presented. Data to support suitability of those analytical methods for their intended use has been provided.

Sufficient detailed strategy for on resin and membrane lifetime validation has been presented. Viral removal studies were performed with new and aged resins.

The shipping verification demonstrates that the shippers can maintain temperature for well beyond the duration required for daclizumab active substance transport, even with worst case variation of external temperature profiles.

Manufacturing process development

Daclizumab active substance has been manufactured at three production bioreactor scales in three different facilities. In addition, daclizumab has been developed at two product concentrations: 100 mg/mL (clinical material) and 150 mg/mL (clinical and commercial material). Both concentrations were provided in a formulation of succinate, sodium chloride, polysorbate 80 and water for injections, pH 6.0.

Daclizumab for clinical studies and commercial use was manufactured using the same NS0 cell line and the same high yield process.

The information provided in support of the actual commercial manufacturing process and control strategy based on initial process development studies, clinical manufacturing experience, process characterization (robustness and range finding) studies, and process and product risk assessments is considered sufficient.

The description of all scaled-down systems used for process development has been provided.

The control strategy is based on product and process risk assessment evaluations conducted to determine the criticality of individual process or product parameters. A Risk Priority Number (RPN) was calculated for Product and Process separately by multiplying the assigned values of Severity, Occurrence, and Detection (RPN = Severity × Occurrence × Detection). High RPN scores are assigned to product or process parameters that have a clear and direct impact on product safety and efficacy, such as adventitious agents and functional potency, or parameters for which there is limited knowledge. The risk assessments followed the Failure Mode and Effects Analysis (FMEA) approach. Correspondence between risk priority number, process parameter classification and risk mitigation was presented.

Changes were introduced during development to support the scale-up of the process. This included changes to the number of seed bioreactors and consequently the purification scale. The changes are considered acceptable.

Likewise, modifications to the daclizumab cell culture parameters were introduced in the commercial manufacturing process. Additional changes were made to the purification steps for the commercial process with experience gained.

No changes were made in the formulation and the overall formulation and filtration process was the same. The minor changes introduced between manufacturing campaigns using the commercial process did not imply a new manufacturing process as the modifications did not change the purification scheme, column cycling strategy, and operating set point conditions. Analytical data was provided from batches manufactured during the clinical and process validation campaigns as well as a post-process validation/conformance campaign run. Results in comparability support this improvement in process control.

Characterisation

The primary amino acid sequence of daclizumab active substance was confirmed, as well as the disulphide linkages. The sixteen cysteine residues are coupled as eight disulphides at locations consistent with those of a typical IgG1 molecule.

Sequence information as well as disulphide linkage analysis obtained from peptide mapping studies allowed consistent identification of close to 100% of predicted sequence.

Charge heterogeneity resulting from heavy chain (HC) N-terminal variants, as well as variable trimming of C-terminal lysine was analysed.

The charge variants distribution gave consistent results for all the validation batches.

Analysis of the N- glycans was performed. The data demonstrated a consistent glycosylation profile across batches, and the presence of glycans that are typically observed on monoclonal antibodies. The predominant glycan species are asialylated core-fucosylated bi-antennary structures. Low abundance of high mannose forms and other non-fucosylated forms is sufficiently controlled.

The secondary and tertiary structural characterization showed consistency between reference standard and the active substance batches for which overlaid spectra were superimposable.

The purity and impurities were also assessed as part of characterization testing, including assessment of aggregate and clipped species.

In addition, biological properties related to the antibody's Fc function were characterized by the binding to the FcγRIIIa and FcγRI receptors and also by the ability of the antibody to induce antibody-dependent cellular cytotoxicity (ADCC). The ability of daclizumab to mediate complement dependent cytotoxicity (CDC) was also tested and the antibody was found to lack CDC activity.

Specification

The control of daclizumab active substance includes a potency assay to measure the binding of daclizumab to its cognate target antigen - CD25 (the alpha subunit of the high affinity IL-2 receptor), and a cell-based functional assay measuring the inhibition of IL-2-induced proliferation of a T-cell line that expresses the IL-2 receptor.

The potency and the functional assay were also used to determine the activity of the isolated charged variants of daclizumab active substance. All of the variants isolated and purified presented equivalent biological activity to daclizumab by both methods.

Process-related impurities that are present or potentially present in the active substance were tested for all the consistency validation and conformance batches as part of process validation. The levels of process-related impurities from the manufacture of the active substance were consistent among the process consistency validation and conformance batches. Also the clearance of these impurities using the commercial manufacturing process was validated. As such, based on the low level results obtained and the calculated removal capacity, none of these impurities are part of the release testing. As the active substance and finished product are the same in terms of formulation and protein concentration, safety assessments apply equally to daclizumab active substance and to finished product.

Microbial testing is performed as in-process controls and as release specifications.

Sufficient information is provided for all tests included in the specifications. Validation of all the methods developed as well as those compendia that require demonstration of suitability was adequately provided.

Justification of specifications

A limited number of batches serve as basis for the definition of the commercial manufacturing specification combining batches produced with two manufacturing processes for which comparability was demonstrated. The justification provided is considered adequate.

Quantitative specifications were defined based on a statistical approach. Certain specifications were defined slightly larger to accommodate expected process variability that might occur when more batches are tested ensuring that future batches will fall within the limits defined.

Stability specifications were set based on the trending of the stability data.

Reference standards

The product quality data from release and extended characterization tests demonstrate that the primary reference standard is representative of the clinical daclizumab batches and thus suitable as a primary reference standard for future working reference standard qualifications.

The selected tests used for working reference standard qualification include relevant key product attributes e.g. primary structure, molecular mass, carbohydrate structure, secondary and tertiary structure, biological activity, purity, and levels of impurities (product-related). The acceptance criteria are

generally the same as for release except for functional biological activity which was set tighter for eligibility purposes.

Stability

The proposed shelf-life at 2-8ºC in the active substance storage containers is acceptable based on the adequate and exhaustive analytical and stability comparability data provided in-between historical and commercial batches produced with different manufacturing process, and in-between commercial batches produced at different stages of the pharmaceutical/clinical development.

For all batches tested at long-term/real conditions compliance with the proposed active substance shelf-life was demonstrated. Validation of the methods selected to be stability indicating was provided.

The post-approval protocol, annual stability protocol and stability commitments have been provided and found to be acceptable.

Container closure system

The container closure system comprises a bioprocess single use container assembled with a filter. Eachables were identified and toxicity studies were performed with scaled-down models. The calculations provided indicate a sufficient safety margin for the intended use.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a colorless to slightly yellow, clear to slightly opalescent liquid, which is essentially free of visible particles and is supplied in a 1 mL sterile, Type 1 glass pre-filled syringe (PFS).

Two presentations, with a nominal amount of 150 mg per dose, are available for subcutaneous administration; a PFS that consists of the syringe assembled with a finger flange and plunger rod, and a pre-filled pen (PFP) which encloses the PFS container closure inside the final assembled PFP.

The daclizumab pre-filled pen (PFP) is a single-use, disposable, injection device that is designed to assist with the delivery of a single dose of daclizumab finished product from the daclizumab pre-filled syringe (PFS).

Satisfactory details of the description and composition of the PFP components have been provided. The safety (biocompatibility) and robustness of the PFP have been satisfactorily established.

The following excipients are contained in the finished product: Sodium succinate, Succinic acid, Sodium chloride, Polysorbate 80, Water for injections.

The functions, concentrations, and characteristics of the components of the formulation including the active substance and each excipient chosen have been adequately described. Daclizumab has been shown to be compatible with the chosen excipients based upon long-term stability data obtained for active substance and finished product.

Pharmaceutical Development

During non-clinical and clinical development, two different concentrations of daclizumab active substance and finished product (100 mg/mL and 150 mg/mL; the latter intended for commercialization) and three different immediate packaging materials for the finished product were described in detail and fully compared. A pre-filled syringe (PFS) was selected as the commercial primary packaging.

As both PFS and PFP presentations proposed for commercialization are identical in respect to the formulated product and the immediate packaging materials, the development of the formulation

performed for the PFS applies also to the PFP presentation. The pre-formulation studies were described in detail taking in account the intended administration route for the finished product, i.e. subcutaneous use. Various variables were considered including buffer pH, buffer concentration, and choice of excipients and their respective concentrations.

Moreover stress tests were also performed to establish the finished product storage conditions which included temperature cycling, freeze-thaw, shaking stress, and light exposure studies.

The results of the light exposure studies on the finished product led to the recommendation of the avoidance of direct exposure of the finished product to light for extended durations.

During development the robustness of the formulation was also assessed by analyzing the impact of small changes in the formulation on stability, namely variations in pH, protein concentration, sodium succinate buffer, sodium chloride and polysorbate 80 concentrations in the presence of stressed conditions (freeze-thaw, shaking, exposure to room temperature and/or light or thermal stress). These stress conditions were chosen on the expected worse-case scenario to mimic potential situations likely to occur during manufacturing and/or shipping.

The only processing occurring during the manufacture of the finished product is the sterile filtration and aseptic filling into syringes of the active substance formulation. Aseptic manufacturing and sterile filtration was selected because the active substance is heat sensitive and thus thermal sterilization could not be used.

Development studies were performed to support the storage, transportation, sterile filtration and PFS filling and included freeze-thaw, temperature cycling, shaking stress, suitability of the fill pump and fill needle, hold times and material compatibility.

Manufacture of the product and process controls

Daclizumab PFS and PFP finished product is manufactured by Biogen (Denmark) Manufacturing ApS.

Each daclizumab PFS lot is manufactured from a single active substance bag. The manufacturing process of finished product consists only of the sterile filtering and aseptic filling of the daclizumab active substance formulation into syringes. Detailed flow charts and descriptions of each operation of the manufacturing process have been provided for the PFS and PFP. No reprocessing steps are planned for the manufacturing of the PFS and assembly of PFP.

Packaging information for the PFS and PFP has been provided, including qualified shipping conditions.

The PFS finished product manufacturing process steps are controlled by controlled parameters, in-process tests and in-process controls. Sterile filtration and aseptic syringe filling were identified as the critical steps of the PFS finished product manufacturing process.

Process validation

The process validation performed for the manufacture of the PFS and PFP finished product, included the following aspects: Process consistency validation, Hold time validation, and aseptic processing validation. Process performance consistency, process characterization, and syringe functionally were also presented.

Process consistency was validated using multiple batches of PFS finished product covering the minimum and maximum PFS lot sizes.

The performed process validation studies overall demonstrate that the PFS manufacturing process is robust and consistently yields finished product that meets the predetermined quality attributes. The analytical procedures used for the validation of the various critical steps of the manufacturing process of

the PFS and PFP finished products were described and adequately validated or the absence of validation justified.

Control of excipients

Adequate information has been provided on the control of the excipients. Sodium succinate, anhydrous is the only non-compendial substance and it is sufficiently described and testing methods provided. The methods have been validated according to ICH Q2(R1).

For all excipients, compendial and non-compendial, Certificates of Analysis issued by the respective vendors/manufacturers and by the active substance/ finished product manufacturer were provided.

Product specification

The finished product specifications share many of the tests used for the control of daclizumab active substance. Specific parameters related to PFS finished product include particulates, microbial and physical safety, as well as PFS functionality.

The release and shelf-life specifications for PFS finished product apply also to PFP. Additionally PFP is tested for device functionality.

Batch analysis was provided for clinical and commercial lots of PFS. The results presented show compliance of all batches of finished product used in clinical studies and manufactured for commercialization with the release specifications in place at the time. Several analytical methods were validated as stability indicating. The tests for purity, microbial safety, and particulates further assure the finished product safety.

Stability of the product

A shelf-life of 36 months at 2°C–8°C is proposed for PFS finished product with an allowance of up to 30 days at a temperature up to 30ºC.

Comparability of commercial with historical batches stability data allowed the conclusion that the stability trends at long-term, accelerated and stressed storage conditions of commercial lots were consistent with data from historical batches and thus the finished product administered to patients in clinical trials is comparable to the one proposed for commercialization.

A photostability study performed with PFS finished product demonstrated that the active substance is sensitive to light when packaged in PFS and that the selected secondary commercial packaging gives adequate protection.

Supply chain temperature cycling and ambient storage simulation studies were performed allowing the establishment of a maximum Time out of Refrigeration.

Based on the stability data presented the proposed storage 2ºC-8ºC for 36 month is considered acceptable. The post-approval stability commitment as well as the annual stability protocol were found to be adequate.

Container closure system

The description of the container closure system is given in sufficient detail and adequate information regarding the materials is presented. Drawings for the packaging components have been provided. Specifications for the syringe barrel and the plunger stopper for the primary packaging have been provided. The syringe barrel and rubber stopper comply with requirements of Ph. Eur. The primary container closure system has been shown to be compatible with the finished product.

The silicone used in the syringe barrel complies with the Ph. Eur. Requirements.

The sterilisation process of the staked needle syringes with rigid needle shield was described and adequately validated. Rubber plungers are also sterilised. Sterilisation of each of the PFS components is performed according to relevant pharmacopoeia and ISO standards.

Two types of device performance test for PFP acceptance are defined.

Medical Device

The pre-filled pen (PFP) is a single-use, disposable, injection device that is designed to assist with the delivery of a single dose of finished product from the pre-filled syringe (PFS).

According to the provisions of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, this product is to be placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and is not reusable. Accordingly, this product is governed by Directive 2001/83/EC. The device element of the product is therefore not CE marked.

Satisfactory details of the description and composition of the PFP components have been provided as has a comparison of the device used in clinical studies compared with that intended for commercialisation. It is accepted that finished product quality attributes will be evaluated on PFP process validation lots to confirm no effect on the finished product quality after assembly into and delivery from the commercial PFP and its comparability with the PFS.

The safety (biocompatibility) and robustness of the PFP have been satisfactorily established. Appropriate details of the assembly process have been provided.

Adventitious agents

In the commercial manufacturing process no material from animal or human origin is used. The risk of TSE contamination from the raw materials used in early development when establishing the cell banks is negligible.

The NS0 cell line used for the production is well characterised. MCB, WCB and EEPCB have been characterised for the absence of contaminating viruses according to ICHQ5A. Extensive tests for rodent viruses, bovine and porcine viruses as well as sterility and mycoplasma have been conducted for the cell banks.

A virus validation study was performed according to CPMP/BWP/268/95 with different model viruses. The capability of several orthogonal process steps (chromatography steps and viral inactivation/filtration steps) to reduce the amount of adventitious viruses has been adequately demonstrated using spiking studies in scaled-down models. Viruses for the clearance studies can be considered to represent a wide range of physico-chemical properties that demonstrates the ability of the system to eliminate the viruses in general.

The control of mycoplasma, bacteria and fungi is performed using compendial methods and at appropriate steps of manufacture. The provided information is considered adequate.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance and finished product was of acceptable quality. The manufacturing processes are well described and properly controlled both for active substance and finished product. Specification limits and analytical methods are suitable to control the quality of the active substance and the finished product. The finished product was well characterised. The stability

program is considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance and the finished product have been appropriately characterised and satisfactory documentation has been provided. The results indicate that the active substance as well as the finished product can be reproducibly manufactured. No major objections have been identified in the initial assessment. The deficiencies and points for clarification were appropriately addressed by the Applicant during the review process.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended an additional point for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Daclizumab targets the alpha subunit (CD25) of the high-affinity receptor for IL-2. By inhibiting IL-2 signalling, it is proposed to reduce T cell proliferation and activation which leads to a reduction in pro-inflammatory autoimmune directed T cell activity in patients with multiple sclerosis. The dataset presented addressed only in vitro pharmacology of daclizumab (Zinbryta).

The product is presented at 150 mg/ml as a solution for injection in a pre-filled syringe or pen for subcutaneous injection in packs containing 1 or 3 syringes or pens. The proposed dose is one subcutaneous injection of 150 mg per month.

2.3.2. Pharmacology

The nonclinical program evaluated test article representative of the drug product (DP) used in clinical development, and DP intended for commercial supply as required.

The pharmacodynamics of daclizumab is well characterized. Daclizuman is a humanized IgG1 monoclonal antibody that binds specifically to CD25, the alpha subunit of the high-affinity interleukin 2(IL-2) receptor. Daclizumab modulates IL-2 signalling, blocking CD25-dependent, high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact. Modulation of IL-2 signalling via antagonism of the high-affinity IL-2 receptor results in distinct immunologic changes that target both activated T cells and ectopic lymphoid aggregates. These effects are hypothesized to reduce both the grey and white matter pathology that underlie the key clinical manifestations of multiple sclerosis (MS) and represent a therapeutic approach for the treatment of MS.

Considering the specific binding of daclizumab to CD25, no secondary pharmacodynamic studies were performed by the Applicant, which was considered acceptable.

Additionally, as there would be limited value in the qualitative and quantitative projection of clinical interactions between therapeutic proteins and drug metabolizing enzymes from in vitro or in vivo nonclinical drug interaction studies, nonclinical drug interaction studies were not conducted, which was also considered acceptable.

Safety pharmacology of daclizumab was performed in cynomolgus monkeys (Macaca fascicularis), by subcutaneous administration. Overall studies showed a good safety profile.

2.3.3. Pharmacokinetics

Pharmacokinetic (PK)/toxicokinetic (TK) profiles of daclizumab were comprehensively evaluated in single dose intravenous IV and single and repeat-dose SC studies (acute, sub-chronic, chronic, reproductive, embryo-foetal, and pre- and post-natal toxicology studies) in cynomolgus monkeys. Daclizuman demonstrated very consistent and linear PK profiles in the 5 to 200 mg dose ranges tested in cynomolgus monkeys over multiple studies, showing predictable PK/TK characteristics of monoclonal antibodies. The overall low incidence of immunogenicity allowed for exclusion of anti-drug antibodies (ADA) positive animals, where the observed decrease of serum daclizumab concentration due to ADA was substantial (>20% of group average), and did not compromise the TK or the toxicological evaluations in any of the studies.

The PK profile of daclizumab, observed after single IV administration, is consistent with that known of mAbs, with a long half-life (t1/2) of (approximately average ~10 days), low systemic clearance (0.167 mL/hr/kg), and a small volume of distribution (54 mL/kg). SC administration of daclizumab, following single and multiple doses, demonstrated slow absorption (time to attain Cmax ~2-3 days), with an approximate dose proportional increase in exposures. Overall, it demonstrated dose proportional linear PK/TK, with no gender difference in any of the PK/TK parameters, and moderate accumulation (~2-fold), predictable based on its terminal half-life (8-16 days range), after repeat SC dosing every 2 weeks. No difference in daclizumab TK parameters were observed in pregnant versus non-pregnant cynomolgus female monkeys and, while the serum ratio of daclizumab in infant: corresponding mother was observed to be 1.0, suggesting good transplacental transfer of daclizumab, the ratio of daclizumab in milk: serum (≤ 0.122%) in lactating cynomolgus monkeys suggested very low excretion of daclizumab via milk in lactating mothers.

A clinical TPDI study in lieu of nonclinical studies was conducted to evaluate the effect of daclizumab on CYP activities. Results indicate that daclizumab has no effect on the activities of the major CYP enzymes.

2.3.4. Toxicology

To evaluate potential systemic effects of daclizumab administration, a single dose GLP intravenous toxicology study was conducted in cynomolgus monkeys (PDL.DAC-06.003/ TR07133), which included a 16-day observation period post-dose. The no- observable-adverse-effect level (NOAEL) for this study was considered to be the highest dose tested, 30 mg/kg.

Repeat-dose toxicology studies were conducted with daclizumab administered SC (clinical and commercial route of administration) q2W.

Two 9-month chronic toxicology studies were conducted. In the first study (PDL.Dac-04.006/TR07185_3), a NOAEL was not determined due to skin findings, and a significant number of control animals (93%) had detectable levels of anti-drug antibodies (ADA). The second study (P019-11-01) was conducted to define a NOAEL. The first study (PDL.Dac-04.006/ TR07185_3) evaluated daclizumab doses of 10, 50, 200 mg/kg and the second study evaluated daclizumab doses of 10, 35, 200 mg/kg. The 35 mg/kg dose was tested in the second study to try to find the highest no observed effect level (NOEL) for a daclizumab-related CNS finding (discussed in more detail below).

The toxicology studies identified the skin and CNS as target organs. The NOAELs for the repeat dose studies were driven by findings in these tissues, depending upon the study. Table 1 describes the findings from the repeat dose toxicology.

Table 1 summary of repeat dose toxicology findings

Study TR Number Study Report Number	Duration of Dosing	Doses (mg/kg)	NOAEL mg/kg	Key Findings (Basis for NOAEL)
TR04236 PDL.Dac-04.002	4-Weeks	5, 50, 125, 200	200[1]	None
TR05395_1 PDL.Dac-04.005	13-Weeks	0, 5, 50, 125, 200	5	Microglial Aggregates
TR07185_3 PDL.Dac-04.006	39-Weeks	0, 10, 50, 200	Not Established	Skin findings
P019-11-01	39-Weeks	0, 10, 35, 200	10	Microglial Aggregates

TR = Technical Report Number
[1]Maximum tolerated dose

In addition to a single IV dose local tolerance study conducted in rabbits, local tissue tolerance was monitored in the repeat dose toxicity studies by clinical observations and histopathology of the injection sites. The repeated SC administration was well tolerated without any adverse injection site reactions.

Daclizumab-related skin changes were observed in both of the 39-week toxicology studies, but not in studies of shorter duration. These findings were characterized grossly as red, dry, scaly areas on body extremities (ears, legs and tail) and orifices (mouth and perianal areas), and on the inguinal, ventral and dorsal areas of the trunk with a microscopic correlate of acanthosis/hyperkeratosis and/or inflammation. These findings were noted in all DAC HYP groups; however, there was no dose-relationship for lesion severity. Although similar findings were present in control animals, they were more prevalent in the DAC HYP groups (i.e., increased incidence, earlier occurrence, multifocal distribution, and longer duration), and as such are considered to be related to the administration of daclizumab. The occurrence of skin findings had a median onset time of 6 months.

Table 2 Incidence of clinical skin findings in the first 39-week study (PDL.Dac-04.006/TR 07185_3)

Dose (mg/kg)	Dry Skin				Red Skin			
	Incidence	%	Onset		Incidence	%	Onset	
			Range (Day)	Average (week)			Range (Day)	Average (week)
0	1/14	7	232	33	8/14	57	13-225	20
10[1]	5/8	63	106-253	25	6/8	75	81-253	22
50	5/8	63	176-241	30	4/8	50	164-218	27
200	8/14	57	106-260	28	12/14	86	81-267	25

[1]One female was humanely euthanized on Study Day 210

Table 3 Incidence of clinical skin findings in the second 39-week study (P019-11-01)

Dose (mg/kg)	Dry Skin				Red Skin			
	Incidence	%	Onset		Incidence	%	Onset	
			Range (Day)	Average (week)			Range (Day)	Average (week)
0	3/12	25	196-240	31	6/12	50	23-260	17
10	3/8	38	196-231	31	4/8	50	44-224	20
35	7/12	58	49-229	17	12/12	100	11-211	11
200	8/12	67	52-229	21	9/12	75	19-110	7

For most treated animals, the skin findings were mild to moderate, were tolerated, and responded to standard veterinary care (cleaning skin areas with chlorhexidine and local application of diaper rash ointment) except for one female animal in a 10 mg/kg dose group in study PDL.Dac- 04.006/ TR07185_3 where they became adverse resulting in an indeterminate NOAEL for this study.

The skin lesions had microscopic correlates of dermal inflammation and epidermal thickening due to acanthosis/hyperkeratosis. Other less common microscopic skin findings were sebaceous gland atrophy, epidermal crusts, and epidermal spongiosis (intercellular edema) with microvesiculation. In the second 39-week study (P019-11-01), in addition to the standard skin samples taken as part of the routine histopathology assessment collected at necropsy, skin biopsies were also collected throughout the study. The additional punch biopsy specimens had the same findings as the routine terminal skin sections taken at necropsy. The etiology of skin findings observed in the chronic (39-Week) repeat dose studies is unclear, but could potentially be related to daclizumab-mediated modulation of IL-2 signaling by immune cell subsets, particularly $CD56^{bright}$ NK cells or regulatory T-cells. Consistent with the hypothesized role of IL-2 modulation contributing to the etiology of the skin findings in monkeys, it is recognized that $CD56^{bright}$ NK cells and regulatory T-cells are involved in a number of skin conditions, including atopic dermatitis [Luci 2012; von Bubnoff 2010; Ilkovitch 2011], psoriasis [Ottaviani 2006; Luci 2012; von Bubnoff 2010; Keijsers 2013], allergic contact dermatitis [Carbone 2010; Lehtimaki 2012].

Skin effects have also been reported in humans administered daclizumab, both in clinical trials with daclizumab (Zinbryta), and with daclizumab (Zenapax) [Oh 2014; Milo 2014]. While the nonclinical studies did not identify a NOAEL for the daclizumab-related skin findings, changes in the skin findings are readily monitorable and manageable in the clinic.

Daclizumab-related CNS findings consisted of microglial aggregates (minimal) in the brain and spinal cord at doses of ≥ 35 mg/kg.

Table 4 Incidence of daclizumab-related microglial aggregates in the brains of cynomolgus monkeys

Study	Dose (mg/kg)	Main Necropsy Males	Main Necropsy Females	Recovery Necropsy Males	Recovery Necropsy Females
Acute Toxicity Study P019-08-01		n=4		n=3	
Single Dose	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	3[a]	NA	1	NA
Two-Doses	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	3[a]	NA	1	NA
Male Reproductive Toxicology Study PDL.Dac-05.001 (5 biweekly doses)		n=5		n=3	
	0	0	NA	0	NA
	10	0	NA	--	NA
	50	2[b]	NA	--	NA
	200	5	NA	0	NA
		n=3	n=3	n=3	n=3
13-Week Toxicity Study PDL.Dac-04.005 (7 biweekly doses)	0	0	0	0[c]	0
	5	0	0	--	--
	50	0	1	--	--
	125	2	2	0	0
	200	2	1	0	0[c]
		n=4	n=4	n=3	n=3
39-Week Toxicity Study PDL.Dac-04.006 (20 biweekly doses)	0	0	0	0	0
	10	0	0[c]	--	--
	50	2	0	--	--
	200	3[b,c]	4[b]	0	1
		n=4	n=4	n=2	n=2
39-Week Toxicity Study P019-11-01 (20 biweekly doses)	0	0	0	0	0
	10	0[d]	0	--	--
	35	0	2	1[b]	1
	200	3[a,c]	3[b]	0	0

[a]Additional microglial aggregate(s) noted in the spinal cord of 2 listed animals.
[b]Additional microglial aggregate(s) noted in the spinal cord of 1 listed animal.
[c]One animal (not listed) had microglial aggregate(s) only in the spinal cord.
[d]A single microglial aggregate in one animal was considered consistent with background occurrence and not test article-related.

Microglial aggregates were observed as small accumulations of cells randomly distributed throughout the grey and white matter of the brain and spinal cord including the cerebral cortex, cerebellum, midbrain and pons, without a preference for a particular site, and all were considered to be of minimal severity. Minimal microhemorrhage was rarely observed associated with the microglial aggregates in animals dosed at 200 mg/kg. A small amount of brown pigment consistent with hemosiderin was observed associated with a microglial aggregate at the recovery necropsy in one 35 mg/kg animal from one of the 39-week studies, suggesting resolution of a previous microhemorrhage. The random distribution of the microglial aggregates does not seem consistent with a neurotoxic effect, and that is in line with de evidence discussed by the applicant. Daclizumab-related CNS findings were not observed at the lowest dose of 10 mg/kg, which provides 7-fold exposure relative to the 150 mg clinical dose.

Table 5 Cynomolgus monkey brain histopathology from toxicity studies with Daclizumab: incidence of microhemorrhage

Study	Dose (mg/kg)	Main Necropsy		Recovery Necropsy	
		Males	Females	Males	Females
Acute Toxicity Study P019-08-01		n=4		n=3	
Single Dose	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	2	NA	0	NA
Two-Doses	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	1	NA	0[1]	NA
39-Week Toxicity Study PDL.Dac-04.006 (20 biweekly doses)		n=4	n=4	n=3	n=3
	0	0	0	0	0
	10	0	0	--	--
	50	0	0	--	--
	200	1	1	0	0
39-Week Toxicity Study P019-11-01 (20 biweekly doses)		n=4	n=4	n=2	n=2
	0	0	0	0	0
	10	0	0	--	--
	35	0	0	0	0[1]
	200	0	1	0	0

[1]A small amount of brown pigment (consistent with hemosiderin) associated with microglial aggregates, suggesting resolution of previous hemorrhage.

To assess the significance of microglial aggregates the applicant pursued different approaches, including:
(1) performing a detailed and dedicated CNS acute neurotoxicity and neurobehavioral study;
(2) review of data from the chronic toxicology studies focusing on expanded histopathology evaluation of CNS tissues and neurobehavioral observations; and,
(3) forming an Expert Pathology Working Group to assess the histologic findings from representative studies.

To assist in the characterization of the CNS findings, an Expert Pathology Working Group (PWG) composed of 6 Board Certified Veterinary Pathologists (Diplomate American College of Veterinary Pathologists, DACVP) was convened to review the CNS data from the 13-week study and the first 39-week study. The PWG concluded that the cellular foci observed in the brain and spinal cords represented aggregates of microglial cells characterized as focal accumulations of mononuclear cells, most of which appeared to be microglial cells within varying regions of the brain parenchyma including the cerebral cortex, cerebellum, midbrain and pons, without a preference for a particular site. They also concluded that the random distribution of the microglial aggregates appear to be inconsistent with a neurotoxic effect and that there was no histologic evidence of neuronal degeneration, axonal fragmentation, or demyelination in association with the microglial aggregates.

The applicant further proposed an understanding of the etiology of the increased microglial aggregates observed in cynomolgus monkeys treated with daclizumab (Zinbryta). In vitro studies were conducted in both human fetal and cynomolgus monkey primary microglial cells to characterize IL-2 receptor expression and daclizumab effects on IL-2 mediated proliferation. These studies demonstrated that cynomolgus and fetal human microglial cell primary cultures express functional intermediate IL- 2 receptors (CD122/CD132), but do not express CD25, the alpha subunit of the high-affinity IL- 2 receptor (R&D/13/953, R&D/13/970). Consistent with the expression of intermediate IL-2 receptors and lack of CD25 expression, primary fetal human and cynomolgus monkey microglial cells signaled in response to

IL-2, but the IL-2 signaling was not affected by blocking CD25, suggesting that microglial aggregates are not a direct consequence of daclizumab binding or a response to injury, but are potentially an indirect effect attributable to increases in IL-2 bioavailability resulting from daclizumabsaturation of CD25 on cells (other than microglial cells) within in the CNS.

The no effect level for daclizumab-related CNS findings (10 mg/kg) provides 7-fold exposure relative to the 150 mg clinical dose, which from a toxicological point of view is acceptable taking into consideration the rationale previously provided.

While effects on liver function tests (LFTs) have been observed in the clinical trials with daclizumab, no clear daclizumab-related effects on the liver were observed in cynomolgus monkeys. This may be due to the low incidence of liver findings in the clinical studies (< 1%).

Genotoxicity and carcinogenicity studies were not conducted with daclizumab. Monoclonal antibodies are not expected to cause genotoxicity by direct interaction with DNA or affect chromosomal structure as tested in the in vitro and in vivo genotoxicity battery, making these types of studies not applicable. There is also no reason to believe that the pharmacological MOA would be associated with an increased risk for carcinogenicity. In fact, blocking the CD25 pathway has been demonstrated to be anti-tumorigenic in mouse tumor models and has been tested as a cancer immunotherapy in humans [Fecci 2006; Sampson 2012; Wainwright 2013; Wang 2012]. Finally, in the clinical experience thus far, the incidence of malignancies was <1% and balanced across the treatment groups, without any specific pattern of malignancies. Taking all of these factors into consideration, it was concluded that daclizumabwould have low risk for carcinogenicity with chronic treatment in humans.

Daclizumabalso poses a low risk for reproductive and developmental toxicity, as there were no adverse effects observed for fertility, embryo-fetal and pre- and post-natal development. Given that daclizumab had no effects on male and female fertility and fetal development and is not expected to alter the immunostasis of pregnancy, it is not anticipated that it will have any generational fertility effects when administered during pregnancy.

Table 6 Reproductive and developmental toxicity studies conducted with daclizumab

Study TR Number; Study Report Number	Type of Study	Duration of Dosing	Doses (mg/kg)	NOAEL[1]	Multiple of Human Exposure[3]
TR07135_2; PDL.Dac-05.001	Male Fertility and Early Embryonic Development[2]	9-Weeks (approximately 60 days to cover all stages of spermatogenesis)	0, 10, 50, 200	200	102
TR06121; PDL.Dac-05.002	Female Fertility and Early Embryonic Development	9-Weeks (approximately 2 menstrual cycles)	0, 10, 50, 200	200	85
TR07122; PDL.Dac-04.003	Pilot Embryo-Fetal Development (Non GLP)	GD 20 – GD 50	200	No maternal or fetal findings	NA
TR07123; PDL.Dac-04.004	Embryo-Fetal Development	GD 20 – GD 50	0, 10, 50, 200	200	140
TC11-033	Pre- and Post-Natal Development	GD 50 – Parturition GD 160 ± 10	0, 50	50	55

NA = Not applicable
[1]Reproductive and Developmental Toxicity NOAEL
[2]Microglial aggregates were observed at ≥ 50 mg/kg
[3] Based on human exposure ($AUC_{0\text{-}28\ days}$; mg*hr/mL) in Clinical Study 205MS302

There were no adverse immunomodulatory effects observed for any of the parameters evaluated. Immunotoxicity was not apparent in repeat dose study findings and in reproductive toxicity studies. While effects on the $CD4^+$ $CD127^{low}$ $FoxP3^+$ T-regulatory cell population have been observed in the clinic this effect has not been observed in cynomolgus monkeys. In normal cynomolgus monkeys, $CD4+/CD127^{low}/-/FoxP3^+$ T-regulatory are rare and only make up approximately 56 to 180 cells/mL [Clark 2010], therefore the lack of an apparent daclizumab-related effect in this cell population may have been related to the limited sampling, cohort sizes and assay sensitivity.

2.3.5. Ecotoxicity / environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*),the environmental risk assessment for proteins may consist of a justification for not submitting ERA studies as they are unlikely to result in significant risk to the environment. The active substance daclizumab is a monoclonal antibody and, therefore, is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The nonclinical characterization of daclizumab included:

a) Pharmacologic characterization of a novel mechanism of action of daclizumab through binding to CD25 and effects on; 1) inhibition of IL-2 induced cell proliferation; 2) inhibition of cytokine secretion by activated T cells; 3) down-modulation of CD25 expression on T cells; 4) in vitro antibody-dependent cellular cytotoxicity (ADCC) and; 5) complement-dependent cytotoxicity (CDC).

b) Detailed pharmacokinetic characterization demonstrating a molecule with consistent and linear pharmacokinetic profile across studies with minimal impact of immunogenicity.

c) Detailed characterization of the safety profile (general, immunological, and developmental and reproductive toxicity) in a comprehensive battery of in vitro investigative and GLP toxicity studies in cynomolgus monkeys.

The target organs identified in the repeat dose toxicity studies are the skin and CNS. Chronic treatment with daclizumab resulted in an increase in skin findings characterized grossly as red, dry, scaly areas with a microscopic correlate of acanthosis/hyperkeratosis and/or inflammation.

While these lesions were also present in controls, their incidence and severity was increased in daclizumab treated animals. There is no safety margin for the daclizumab-related skin findings, but this risk is offset in the clinical setting as skin findings can be appropriately monitored and managed as part of clinical practice.

The daclizumab-related increase in microglial aggregates was characterized across several studies. Evidence from investigative studies indicated that they might not represent a neurotoxic response but rather a physiological response due to increases in IL-2 concentrations that occur when daclizumabDAC HYP saturates CD25 expressing tissues within the CNS of cynomolgus monkeys at exposures which are 27-fold greater than the clinical exposure.

2.3.7. Conclusion on the non-clinical aspects

The nonclinical pharmacology, pharmacokinetics, and toxicology studies described provide the required justification for the use of daclizumab when administered SC to MS patients monthly at doses of 150 mg.

2.4. Clinical aspects

2.4.1. Introduction

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling. This application was submitted to support the approval of Daclizumab High Yield Process (DAC HYP), also known as Zinbryta, a new form of daclizumab, as a disease-modifying therapy (DMT) for the treatment of patients with relapsing forms of multiple sclerosis (RMS).

Daclizumab (DAC-Nutley) was first approved as Zenapax 5 mg/ml concentrate for solution for infusion for the prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation; this medicinal product is no longer authorised. The posology in adult and paediatric patients was 1 mg/kg with the dose added to 50 ml of sterile 0.9% saline solution to be administered intravenously over 15 minutes.

Biogen Idec has evaluated daclizumab High Yield Process for use in relapsing forms of multiple sclerosis in a single Phase 2 study (205MS201) and one Phase 3 studies (205MS301), both with extension studies and a number of clinical pharmacology studies.

- The Overview of the Clinical Development of Daclizumab (Zinbryta) in MS is presented in the below chart:

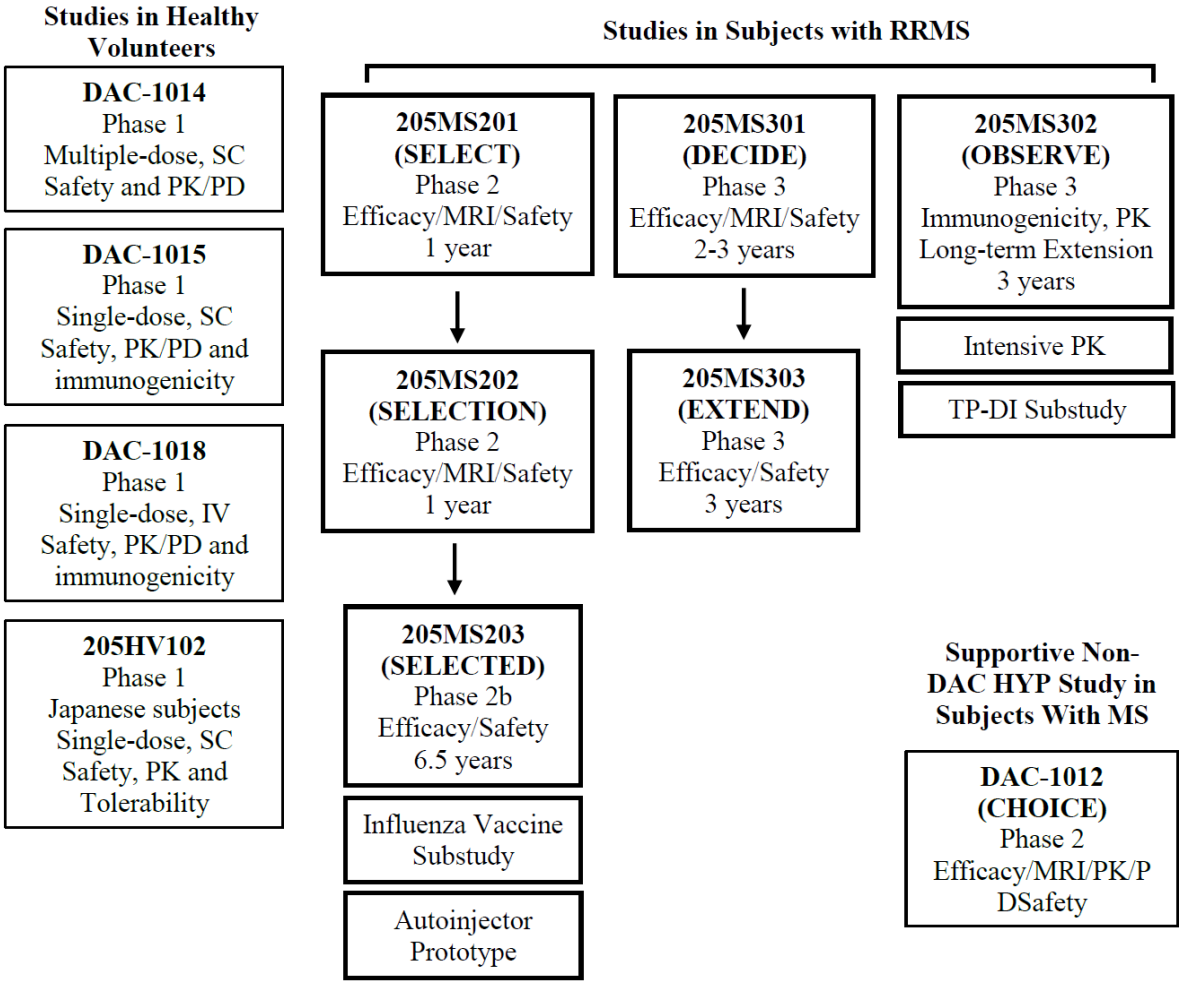


Figure 1 Overview of the Clinical Development of daclizumab (Zinbryta).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

Table 7 Overview of studies

Study No.	Study Description	Number in the Safety Population			Objective
		Placebo	DAC HYP	IFN β-1a	
Placebo-Controlled Study					
205MS201	Double-blind, placebo-controlled, dose-ranging study in RRMS subjects DAC HYP 150 mg or 300 mg SC or Placebo, 1 dose every 4 weeks for 52 weeks	204	417	--	Evaluation of the safety and efficacy
Active-Controlled Study					
205MS301	Double-blind, parallel group, active-controlled study in RRMS subjects DAC HYP 150 mg SC once every 4 weeks for 96 to 144 weeks IFN β-1a IM 30 µg once weekly for 96 to 144 weeks	--	919	922	Evaluation of the safety and efficacy
Dose-Blinded Study					
205MS202	Double-blind extension study of 205MS201 Placebo subjects in 205MS201 were assigned to either DAC HYP 150 mg or DAC HYP 300 mg SC once every 4 weeks for 52 weeks DAC HYP subjects in 205MS201 were assigned to either continue at their current dose of DAC HYP (150 mg or 300 mg) or receive 5 doses of placebo during a washout period, followed by 8 DAC HYP doses (150 mg or 300 mg)	--	517 (170 new exposures)	--	Evaluation of the efficacy safety and immunogenicity of extended treatment with DAC HYP
Uncontrolled Studies					
205MS203	Single-arm, open-label extension study of 205MS202 DAC HYP 150 mg SC every 4 weeks for up to 6.5 years in subjects who completed treatment in 205MS202	--	410 (no new exposures)	--	Evaluation of long-term safety and efficacy
205MS302	Single-arm, open-label study DAC HYP injections were given using the PFS every 4 weeks over an initial 24-week treatment period (for a total of 6 doses), followed by a 20-week washout period After completion of the washout period, eligible subjects had the option to resume open-label treatment with DAC HYP 150 mg every 4 weeks for up to 3 years (or subjects could elect to complete the study through Week 44 only)	--	133 (n=113 in the main study phase)	--	Evaluation of the immunogenicity of DAC HYP using a PFS

Table 8 Overview of studies (ctd.)

205MS303	Single-arm, open-label extension study of 205MS301 DAC HYP 150 mg SC once every 4 weeks for 33 mean cumulative doses	--	308 (146 new exposures)	--	Evaluation of long-term safety and efficacy
Substudies[a]					
205MS203	Open-label substudy comparing the use of the PFS and autoinjector DAC HYP 150 mg SC once every 4 weeks for 4 doses using autoinjector, and once every 4 weeks using PFS or autoinjector for approximately 16 weeks	--	60	--	Assessment of the PK of the single-use autoinjector compared with the PFS
205MS203	Open-label substudy evaluating the immune response to the trivalent influenza vaccine DAC HYP 150 mg SC once every 4 weeks 2013-2014 trivalent influenza vaccine, 1 dose	--	91 (90 received vaccine)	--	Assessment of the impact of DAC HYP treatment on response to the seasonal influenza vaccine
205MS302	Open-label substudy evaluating the PK and PD from the PFS Intensive PK sampling was performed after doses 1 and 6.	--	26	--	--
205MS302	Open-label therapeutic protein-drug interaction (TP-DI) substudy evaluating the PK of probe drugs for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A). DAC HYP 150 mg SC once every 4 weeks for 6 doses	--	20	--	--
Subjects in the Safety Population for DAC HYP MS Studies[b]		204	1785[c]	922	--

Source: CSRs 205MS201, 205MS301, 205MS202, 205MS203, 205MS302, 205MS303; Appendix Table 14.
CSR = clinical study report; CYP = cytochrome P450; DAC HYP = daclizumab high yield process; IFN β-1a = interferon beta-1a; IV = intravenous; IM = intramuscular; MS = multiple sclerosis; PD = pharmacodynamics; PFS = prefilled syringe; PK = pharmacokinetics; RRMS = relapsing-remitting multiple sclerosis
[a] Substudy subjects are counted in the substudy as well as the parent study.
[b] Subjects are counted in more than 1 column as appropriate.
[c] Total subjects in pooled safety population.

2.4.2. Pharmacokinetics

The pharmacokinetics (PK) of daclizumab have been characterized utilizing intensive/serial sampling from 4 Phase 1 studies in healthy volunteers (HVs) and 1 immunogenicity study in subjects with multiple sclerosis (MS), and using sparse sampling from Phase 2 and 3 studies in subjects with MS. In addition, the therapeutic protein-drug interaction (TP-DI) potential for daclizumab was investigated in subjects with MS (see Table 9 and Table 10).

Table 9 Summary of Daclizumab (Zinbryta) Clinical Pharmacology studies (healthy volunteers)

Study Identifier	Study Objectives	Study Design	Test Product; Dosage Regimen; Route of Administration	Planned Treatment Period	Number of Subjects Enrolled; Completed	Planned Age range
PK/PD Studies in Healthy Volunteers						
DAC-1015	To determine the safety, tolerability, PK, PD, and immunogenicity of SC DAC HYP	Single-dose, double-blind, placebo-controlled, dose-escalating	DAC HYP, single dose 50 mg SC (n = 7) 150 mg SC (n = 8) 300 mg SC (n = 8) Placebo SC (n = 10)[a]	Single dose	34 enrolled; 32 completed	18 to 75 years, inclusive
DAC-1014	To determine the safety, tolerability, PK, PD, and immunogenicity of multiple doses of DAC HYP administered by SC injection	Multiple-dose, randomized, double-blind, placebo-controlled	DAC HYP, multiple dose 200 mg SC every 2 weeks × 9 doses (n = 12) 200 mg SC loading dose + 100 mg SC every 2 weeks × 8 doses (n = 12) Placebo SC 9 doses (n = 8)	16 weeks	32 enrolled; 27 completed[b]	18 to 65 years, inclusive
DAC-1018	To determine the safety, tolerability, PK, PD, and immunogenicity of IV DAC HYP	Single-dose, double-blind, placebo-controlled, dose-escalating	DAC HYP, single dose 200 mg IV (n = 12) 400 mg IV (n = 12) Placebo IV (n = 7)	Single dose	31 enrolled; 30 completed	18 to 65 years
205HV102	To evaluate the PK, safety, and tolerability of DAC HYP administered as a single SC dose in Japanese and Caucasian adult HVs	Single-dose, single-blind	DAC HYP, single dose 75 mg SC (n = 28; 14 per ethnic group) 150 mg SC (n = 28; 14 per ethnic group)	Single dose	56 enrolled; 56 completed	18 to 55 years, inclusive

Table 10 Summary of daclizumab (Zinbryta) Clinical Pharmacology studies (MS patients)

Study Identifier	Study Objectives	Study Design	Test Product; Dosage Regimen; Route of Administration	Planned Treatment Period	Number of Subjects Enrolled; Completed	Planned Age range
PK and PD Studies in MS Subjects						
205MS203 *Autoinjector PK Substudy*	To compare the systemic exposure of daclizumab following SC administration of 150 mg DAC HYP using the single-use autoinjector (PFP) to the systemic exposure following manual PFS injection	Open-label, parallel design	DAC HYP 150 mg SC from a PFS by either manual injection or by autoinjector every 4 weeks for 4 doses	16 weeks	60 enrolled; 60 completed	18 to 55 years, inclusive
205MS302 *Intensive PK Substudy*	To characterize the PK of DAC HYP following single and multiple doses of SC DAC HYP administered by the PFS in a subset of subjects with RRMS	Single-arm, open-label	DAC HYP 150 mg SC by PFS every 4 weeks for 6 doses	24 weeks	26 enrolled; 25 completed	18 to 65 years, inclusive
205MS302 *TP-DI Substudy*	To evaluate the effect of DAC HYP on the PK of probe substrates for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in MS subjects	Single-arm, open-label study)	DAC HYP 150 mg SC by PFS every 4 weeks for 3 doses	12 weeks	20 enrolled; 20 completed	18 to 65 years, inclusive

CYP=cytochrome P450; DAC HYP=Daclizumab High-Yield Process; HV = healthy volunteer; IV=intravenous; MS=multiple sclerosis; PD=pharmacodynamic; PFS=prefilled syringe; PK=pharmacokinetic; RRMS=relapsing-remitting multiple sclerosis; SC=subcutaneous; TP-DI=therapeutic protein-drug interaction

[a]One subject was assigned to placebo but had measurable daclizumab concentrations in the PK samples at every timepoint. Therefore, this subject is not counted as a placebo subject.

[b]Twenty-seven of 32 subjects completed the 16-week treatment period, but none of these subjects received all of the planned doses because of a temporary suspension of dosing for a safety evaluation.

Pharmacokinetic Properties of Daclizumab (Zinbryta)

Daclizumab exhibits PK characteristics of a typical IgG1 mAb. Following SC administration, daclizumab absorption is believed to be mediated primarily via the lymphatic system with an observed Tmax of approximately 1 week. Daclizumab disposition is well characterized by a 2-compartment model with a first-order absorption and elimination. Linear PK was observed for doses greater than 100 mg, with the estimated absolute bioavailability for subcutaneous administration of 90%. A small volume of distribution was observed, indicating daclizumab is largely confined to the vascular and interstitial spaces. Daclizumab is not expected to undergo metabolism by hepatic enzymes such as CYP isoenzymes or renal elimination. A low systemic clearance and long elimination half-life (approximately 3 weeks) were observed. Steady state was achieved by Week 16 dosing daclizumab 150 mg SC every 4 weeks, with the resulting mean steady-state peak-to-trough concentration ratio of approximately 2 and an AUC accumulation ratio of approximately 2.5.

Single-Dose Pharmacokinetics of Daclizumab (Zinbryta)

A single-dose IV study was conducted in HVs at daclizumab doses of 200 mg and 400 mg (Study DAC-1018). Following a 30-minute IV infusion, daclizumab exhibited a low clearance (mean CL 10 mL/h), a low steady-state volume of distribution (mean Vss values from 5.89 to 6.53 L), and long elimination half-life (mean t1/2 values from 18 to 20 days). Dose-proportional increase in exposure was observed between 200 mg and 400 mg. Single-dose SC studies were performed in HVs at daclizumab doses of 50 mg, 75 mg, 150 mg, and 300 mg. Median Tmax was 6 to 7 days. Mean Cmax and AUC0-inf values increased more than dose proportionally between 50 and 150 mg and dose proportionally between 150 and 300 mg. A relatively long elimination half-life (mean t1/2 values from 17.2 to 24.9 days) was observed.

Multiple-Dose Pharmacokinetics of Daclizumab (Zinbryta)

Multiple-dose PK of DAC HYP was evaluated in HVs (DAC-1014) for 2 different dosing regimens: 200 mg SC every 2 weeks, and a 200 mg SC loading dose followed by 100 mg every 2 weeks. A total of 9 SC administrations over 16 weeks were planned for both regimens. However, dosing during the study was interrupted because of a temporary treatment suspension. As a result, none of the 24 daclizumab subjects received all 9 planned doses; 17 of 24 of daclizumab subjects received 7 or 8 doses. The daclizumab PK profile after multiple SC administrations showed a slow absorption (Tmax approximately 7 days after the first dose) and a long elimination half-life (approximately 15 days). Steady-state AUCtau values were estimated to be 8 mg.h/mL (100 mg every 2 weeks) and 16 mg.h/mL (200 mg every 2 weeks). Multiple-dose PK in MS subjects was characterized for daclizumab 150 mg SC every 4 weeks by PFS in 2 studies (302 and 203). PK parameters determined from these studies were comparable. Daclizumab PK following multiple SC administrations showed a slow absorption profile, with a median Tmax of approximately 5 days and a long elimination half-life (t1/2) of approximately 22 days. Daclizumab pre-dose concentrations in Study 302 revealed that steady state was reached by Week 16 of dosing (or Dose 4), which is consistent with the half-life. Repeated dosing of daclizumab every 4 weeks resulted in an approximately 2.5-fold drug accumulation at steady state.

Daclizumab (Zinbryta) Population Pharmacokinetics

Population PK of daclizumab were characterized using data from the Phase 1 studies in HVs who received daclizumab 50 to 300 mg SC (Study DAC-1014, Study DAC-1015) or 200 and 400 mg IV (Study DAC-1018), and from the Phase 2 and 3 studies in MS subjects who received 150 or 300 mg SC every 4 weeks (Study 201, Study 202, Study 302, and Study 301).

Population PK modelling was conducted using NONMEM 7 (version 2.0) with first-order conditional estimation with interaction (FOCEI) method. Perl Speaks NONMEM (PsN, Version 3.5.3) was used to conduct bootstrap and a visual predictive check (VPC) for model qualification. The program Xpose4 (version 4.3.2, Pharmacometrics Research Group, Uppsala University, Sweden), a module written for the statistical program R, was used to assist diagnostics.

Model development was performed in 2 stages: The initial model was developed without data from Study 301, and the final model was updated with data from Study 301 to obtain the final parameter estimates. Covariate modelling was performed in a stepwise forward addition and backward elimination manner. Examined covariates included body weight, age, sex, dose group, NAb, non-NAb, baseline percentages of CD4+ T cells staining positive for CD25, and baseline absolute CD25+CD4+ T cell counts. Race was not tested because of the limited sample size for races other than White.

A 2-compartment model with first-order absorption and elimination described the daclizumab PK well in both HVs and MS subjects. The point estimates from the final model and the median parameter estimates from the bootstrap datasets were similar.

For a typical subject with a body weight of 68 kg, clearance was 0.212 L/day, central and peripheral volumes of distribution (V2 and V3) were 3.92 L and 2.42 L, respectively, with a moderate IIV between 27% and 51%. The SC absorption half-life was 5 days with an absorption lag time of 1.61 hours, and SC bioavailability was 88% for the 100 to 300 mg dose levels and 55% for the 50 mg dose level. The terminal half-life was 21.4 days. Due to the low number of subjects with PK data usable to quantify the IOV of daclizumab, a model development with the full dataset was not possible. As such, the applicant provided an evaluation of the IOV in a subset of 26 subjects from the intensive PK subgroup in OBSERVE study. In this subset, IOV variability in CL and V2 (around 20%) was lower than the IIV.

Statistically significant covariates for daclizumab PK included body weight and the presence of NAbs. Body weight was a significant covariate for CL and V2, with exponents of 0.87 and 1.12, respectively, thereby explaining 37% and 27% of the IIV for CL and V2, respectively. Time-varying NAb-positive status increased daclizumab CL by 19%. The impact of these 2 covariate effects does not appear to be clinically relevant based on the following observations. In Study 301, no meaningful differences in safety or efficacy were observed among the subgroups by body weight quartile. There was no discernible impact of immunogenicity status (ADA or NAb) on the efficacy or safety profile of daclizumab.

Factors Influencing Pharmacokinetics and Special Populations

Daclizumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Therefore, no studies were conducted to evaluate daclizumab PK in patients with hepatic or renal impairment. However, the effect of ALT (similarly for AST) elevation on the pharmacokinetics of daclizumab (clearance, CL) was tested as a time-varying covariate within the context of the population PK model developed for daclizumab. According to these analyses, liver enzyme elevation was estimated to minimally increase clearance of daclizumab (~10%). This does not seem to be physiologically meaningful because in general, an adverse effect on the liver is expected to impair drug clearance instead of enhancing it. Given the small magnitude of estimated effect and almost no reduction in the overall inter-subject variability in clearance, it can be concluded that liver enzyme elevation is unlikely to have any clinically meaningful detrimental effect on the clearance of daclizumab. No apparent PK differences were observed between Japanese and Caucasian subjects following a single-dose administration of daclizumab 75 mg or 150 mg SC. Population PK analysis indicated that the PK parameters of daclizumab were not influenced by age (range 18 to 66 years) or sex of adult subjects. Population PK analysis showed that body weight was a significant covariate for daclizumabCL and central volume of distribution, explaining 37% and 27%, respectively, of the estimated IIV for these two parameters. Time-varying

NAb-positive status increased daclizumab CL by 19% on average. However, the impact of these 2 covariate effects on daclizumab exposure does not appear to be clinically relevant.

Overall, the pharmacokinetics of daclizumab are well characterized, and well described in the SmPC.

2.4.3. Pharmacodynamics

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling that is important for lymphocyte activation.

The immunogenicity of daclizumab was characterized as follows:

The incidence of immunogenicity to daclizumab 150 mg after multiple dosing of MS subjects with daclizumab showed the following results:

- Treatment-emergent ADAs were observed in 4% and 19% of evaluable subjects during the study in Study 201 and Study 301, respectively. Treatment-emergent neutralizing antibodies (NAbs) were observed in 3% and 8% of evaluable subjects in Study 201 and Study 301, respectively. The differences in the incidences of immunogenicity between the 2 studies appeared to be due primarily to more frequent immunogenicity testing at early timepoints and to a more sensitive assay being used in Study 301 than in Study 201;

- Pre-existing ADA reactivity at Baseline was observed in 4% and 6% of evaluable subjects in Study 201 and Study 301, respectively;
- The majority of ADA reactivity to daclizumab occurred early during treatment, and this reactivity decreased with continuing daclizumab treatment. ADA titers observed were generally low with only 3 persistent subjects in Study 301 reaching a titer of >1920 (highest titer observed in the transient category);
- The majority of subjects that exhibited immunogenicity showed transient responses;
- There was increased detection of observed immunogenicity during the washout of daclizumab;
- The immunogenicity profile of daclizumab administered by SC injection using the PFS was comparable to daclizumab administered from vials;
- Time-varying NAb status increased daclizumab clearance by 19% on average. However, the impact does not appear to be clinically relevant since there was no discernible impact of immunogenicity status on the efficacy, safety, or PD profile of daclizumab.

No relationship has been established between daclizumab plasma concentrations and the efficacy parameters use in the clinical studies, whether for relapses or MRI imaging. No relationship could be found either between daclizumab exposure and safety. No specific difference was seen with regards to PD depending on race.

2.4.4. Discussion and conclusions on clinical pharmacology.

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling that is important for lymphocyte activation.

Generally the PK and PD of daclizumab were well described and no additional measures are considered necessary.

2.5. Clinical efficacy

The clinical efficacy of daclizumab in the proposed indication was evaluated in three clinical trial:

- DAC-1012 a 6-month Phase 2 dose ranging study with DAC Penzberg
- Study 205MS201 a 1 year phase 2 Efficacy/MRI/safety study with DAC-HYP 150 mg and 300 mg SC every 4 weeks, with one year extension (study 202)
- Study 301, a Phase 3 study over 3 years with DAC-HYP 150mg SC every 4 weeks

In addition there were two extension studies form Study 205MS201, i.e. Study 202 (one year extension, completed) and Study 203, extension to Study 202, ongoing.

2.5.1. Dose response study(ies) and Main study(ies)

2.5.1.1. DAC-1012

DAC-1012 was a Phase 2 randomized, double-blind, placebo-controlled, multi-center, proof-of-concept, dose-ranging, parallel-design study comparing daclizumab and placebo in subjects receiving concurrent IFN β therapy for active, relapsing forms of MS. In this study, 2 regimens of DAC Penzberg (an investigational form of daclizumab) administered SC over a 24-week period (20 weeks plus 4 weeks follow-up) were compared to placebo; follow-up duration was 48 weeks.

DAC Penzberg is a different form of daclizumab with a different glycation; it was developed before daclizumab.

Patient population

Males or females, 18 to 55 years of age, inclusive; diagnosis of MS by McDonald criteria; score of ≤5.0 on the EDSS; taking a stable IFN-beta regimen (defined as at least 6 months on the same dose of the same drug product); had at least one MS relapse while taking stable IFN-beta regimen, or had a qualifying MRI, showing at least one confirmed Gd-CEL of the brain or spinal cord while taking stable IFN-beta regimen.

DAC-1012 was conducted in 51 investigational sites in the US, Canada and the European Union (Germany, Italy and Spain).

288 patients were screened and 230 were randomized; 214 (93%) completed 24 weeks of treatment and 194 (84%) completed follow-up through Week 72.

Treatment

The 2 DAC Penzberg regimens were 2 mg/kg every 2 weeks for a total of 11 doses (high dose) and 1 mg/kg every 4 weeks for a total of 6 doses (low dose). The study consisted of a 24-week treatment period, followed by a 48-week washout period, during which study drug was not administered, but continued on IFN-beta therapy for at least 5 months of the 48 weeks).

The doses of 1 mg/kg and 2 mg/kg were extrapolated from animal and clinical data.

Objectives: The primary objective was to evaluate the efficacy of daclizumab in patients who had active, relapsing forms of multiple sclerosis (MS) and were concurrently on interferon-beta (IFN-beta) therapy.

The secondary objectives were safety, PK and PD and immunogenicity (i.e., development of antibodies to daclizumab).

The primary efficacy endpoint was the total number of new or enlarged gadolinium contrast enhancing lesions (Gd-CELs) on monthly brain magnetic resonance imaging (MRI) collected between Weeks 8 to 24 in daclizumab versus placebo-treated patients. An enlarged lesion was defined as a greater than 50% increase if the lesion was <5 mm in diameter, and a 20% increase if the lesion was ≥5 mm in diameter; the enlargement was estimated visually and by the judgment of the reader.

Compared with placebo the effect of DAC Penzberg on reducing new Gd-enhancing lesions, the primary endpoint of Study DAC-1012, was robust and statistically significant in the high-dose arm 2 mg/kg every 2 weeks (p=0.0038), but was marginal and not statistically significant in the low-dose arm 1 mg/kg every 4 weeks (p=0.5138). Safety was similar between the low-dose and high-dose regimens.

Based on the results of Study DAC-1012, two daclizumab dosing regimens (150 mg and 300 mg SC every 4 weeks) were selected for further evaluation in Study 205MS201 based on the following considerations:

- The low-dose regimen from Study DAC-1012, which is approximately equivalent to a fixed-dose regimen of 75 mg SC every 4 weeks, was considered to be below the lowest efficacious dose. Furthermore, this regimen showed no evidence for an improved safety profile compared to the high-dose regimen. Therefore, daclizumab doses that were expected to provide similar exposures were not evaluated further.
- Daclizumab 300 mg SC every 4 weeks was projected to be approximately equal to the highest efficacious dose (2 mg/kg SC every 2 weeks) evaluated in Study DAC-1012.
- Daclizumab150 mg SC every 4 weeks was projected to be a lowest efficacious dose since it was between the low-dose and high-dose arms in Study DAC-1012.

2.5.1.2. Studies 205MS201 and 205MS301

Study 205MS201 was a double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of daclizumab as a monotherapy treatment in subjects with RRMS. Two daclizumab dose regimens were studied: daclizumab 150 mg and 300 mg administered by SC injection once every 4 weeks. The study consisted of a 52-week (Weeks 0 through 52), double-blind, placebo-controlled, safety and efficacy treatment phase; and a 20-week (Weeks 52 through 72), double-blind, follow-up phase for subjects who did not enter the extension study (Study 202). The primary endpoint of Study 205MS201 was the annualized relapse rate between baseline and Week 52.

Upon completion of the 12-month treatment period in Study 205MS201, subjects were eligible to complete up to an additional 12 months of treatment with daclizumab in a double-blind extension (Study 205MS202 referred to as 202), which was completed in 2012. Study 202 also assessed the effects of daclizumab washout in some subjects who were treated with daclizumab in Study 205MS201. Subjects completing Study 202 could continue long-term therapy with open-label daclizumabin the ongoing extension Study 203, which is evaluating the long-term safety and efficacy of daclizumab monotherapy for an additional 6.5 years.

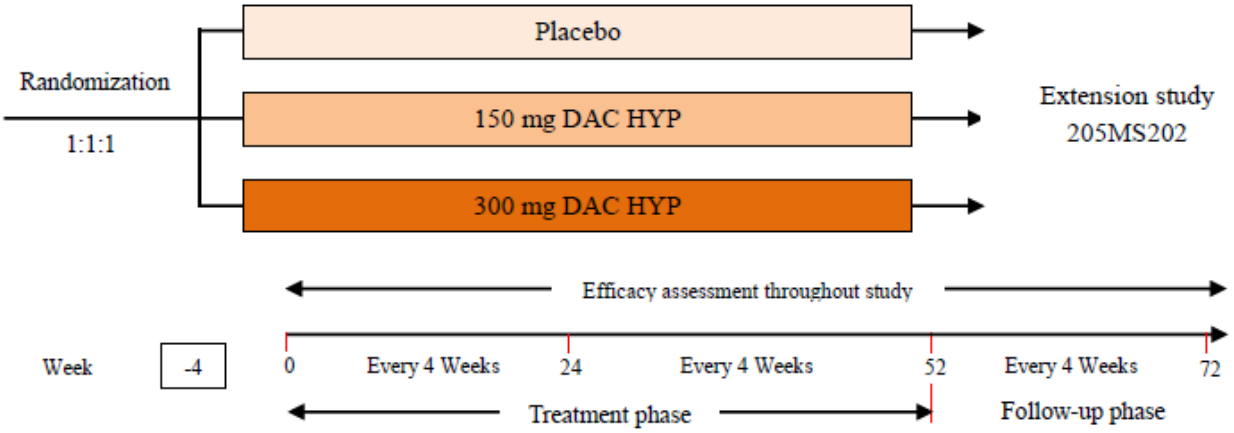


Figure 2 Design of study 205MS201

Study 205MS301 was a double-blind, randomized, parallel-group, monotherapy, active-control study to determine the efficacy and safety of daclizumab versus interferon beta-1a (IFN β-1a) in patients with RRMS. Two treatment groups were studied: Daclizumab 150 mg SC once every 4 weeks for 96 to 144 weeks and IFN β-1a 30 µg intramuscular (IM) injection once weekly for 96 to 144 weeks. Subjects were treated in this study for at least 96 weeks but no more than 144 weeks.

The primary efficacy endpoint of the study was the annualized relapse rate. Subjects who completed the treatment period and who met study entry criteria were eligible to enrol in the open-label extension (Study 303) to either continue (subjects treated with daclizumab in Study 301) or start (subjects treated with IFN β-1a in Study 301) dosing with daclizumab. Those subjects who did not enrol in the open-label extension study remained in a 24-week, blinded, post-dosing, safety follow-up period.

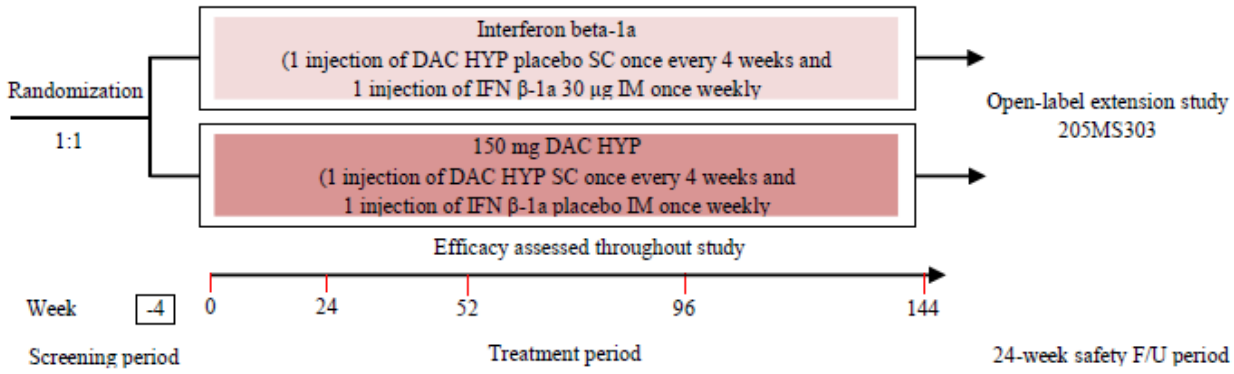


Figure 3 Design of Study 205MS301

- The following tables summarize the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment sections.

Table 11 Summary of efficacy for trial 205MS201

Title: Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Safety and Efficacy of Daclizumab (DAC HYP/Zinbryta) as a Monotherapy Treatment in Subjects with Relapsing-Remitting Multiple Sclerosis			
Study identifier	205MS201		
Design	Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1 year not applicable 1 year (205MS202) + up to 6.5 years (205MS203)
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo SC every 4 weeks, for 1 year, 204 pts
	Daclizumab150mg		Daclizumab150 mg SC every 4 weeks, for 1 year, 208 pts
	Daclizumab300mg		Daclizumab300 mg SC every 4 weeks, for 1 year, 209 pts
Endpoints and definitions	Primary endpoint	Annualized relapse rate	Annualized relapse rate
	Secondary endpoint	new Gd+ lesions	Number of new Gd+ lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 in a subset of subjects
	Secondary endpoint	newly enlarging T2 hyperintense lesions	Number of new or newly enlarging T2 hyperintense lesions at Week 52
	Secondary endpoint	% relapsing subjects	Proportion of relapsing subjects between baseline and Week 52
	Secondary endpoint	Change in MSIS-29 physical score	Change in MSIS-29 physical score at Week 52 compared to baseline
Database lock	04 November 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Daclizumab150mg	Daclizumab300mg
	Number of subject	196	201	203
	Primary endpoint			
	Primary endpoint Annualized relapse rate (adjusted)	0.458	0.211	0.230
	(95% CI)	(0.370-0.566)	(0.155-0.287)	(0.172-0.308)
	Secondary endpoints			

	Adjusted mean number of new Gd lesions (week 8 to 24)	4.79	1.46	1.03
	(95% CI)	(3.56, 6.43)	(1.05, 2.03)	(0.73, 1,46)
	New or Newly Enlarging T2 Hyperintense Lesions at Weeks 52 (Adjusted mean)	8.13	2.42	1.73
	(95% CI)	(6.65, 9.94)	(1.96, 2.99)	(1.39-2.15)
	Estimated proportion of subjects relapsed by 52 weeks	0.36	0.19	0.20
	Unadjusted Mean change from baseline in MSIS-29 physical score at week 52 (SD)	3.0 (13.52)	-1.0 (11.80)	1.4 (13.53)
	Estimated proportion progressed (sustained increase in EDSS for 12 weeks) at week 52	0.133	0.059	0.078
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 52	0.111	0.026	0.068

Effect estimate per comparison	Annualized relapse rate	Comparison groups	Placebo vs. Daclizumab 150 mg
		ARR ratio	0.461
		95% CI	(0.318 0.668)
		P-value	P< 0.0001
	Adjusted mean number of new Gd lesions (week 8 to 24)		Placebo vs. Daclizumab150 mg
		Lesion mean ratio	0.305
		95% CI	0.196, 0.476
		P-value	P < 0.0001
	New or Newly Enlarging T2 Hyperintense Lesions at Weeks 52 (Adjusted mean)		Placebo vs. Daclizumab 150 mg
		Lesion mean ratio	0.298
		95% CI	(0.221, 0.409)
		P-value	P <0.0001
	Estimated proportion of subjects relapsed	Comparison groups	Placebo vs. Daclizumab 150 mg
		Hazard ratio	0.45

	by 52 weeks	95% CI	(0.30, 0.67)
		P-value	P< 0.0001
	Unadjusted Mean change from baseline in MSIS-29 physical score at week 52	Comparison groups	Placebo vs. Daclizumab 150 mg
		Relative mean change	-4.27
			-6.76, -1.78
			0.0008
	Estimated proportion progressed (sustained increase in EDSS for 12 weeks) at week 52	Comparison groups	Daclizumab 150mg vs. placebo
		Hazard ratio	0.43
		95% CI	(0.21, 0.88)
		P-value	P=0.0211
		Comparison groups	Daclizumab 300mg vs. placebo
		Hazard ratio	0.57
		95% CI	(0.30, 1.09)
		P-value	p=0.0905
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 52	Comparison groups	Daclizumab 150mg vs. placebo
		Hazard ratio	0.24
		95% CI	(0.09, 0.63)
		P-value	P=0.0037
		Comparison groups	Daclizumab 300mg vs. placebo
		Hazard ratio	0.60
		95% CI	(0.30, 1.20)
		P-value	p=0.1487

Table 12 Summary of efficacy for trial 205MS301

Title: Multicenter, Double-blind, Randomized, Parallel-group, Monotherapy, Active-control Study to Determine the Efficacy and Safety of Daclizumab High Yield Process (DAC HYP) versus Avonex® (Interferon β-1a) in Patients with Relapsing-Remitting Multiple Sclerosis			
Study identifier	205MS301		
Design	Multicenter, double-blind, randomized, parallel-group, monotherapy, active-control study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96-144 weeks not applicable Up to 5 years (205MS303)
Hypothesis	Superiority		
Treatments groups	IFN β-1a 30 µg		IFN β-1a 30 µg IM every week, for96-144 weeks, 922 pts
	DAC HYP 150 mg		Daclizumab150 mg SC every 4 weeks, for96-144 weeks, 919 pts
Endpoints and definitions	Primary endpoint	Annualized relapse rate	Annualized relapse rate
	Secondary endpoint	newly enlarging T2 hyperintense lesions	Number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks
	Secondary endpoint	% confirmed disability progression	Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 12 weeks or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks
	Secondary endpoint	% relapse-free	Proportion of subjects who are relapse-free
	Secondary endpoint	% of subjects with a significant worsening the MSIS-29 Physical Impact score	Proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks
Database lock	16 September 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat – all patients randomised and treated		
Descriptive statistics and estimate variability	Treatment group	IFN β-1a 30 µg	Daclizumab 150 mg
	Number of subject	922	919

	Primary endpoint		
	Annualized relapse rate (adjusted)	0.393	0.216
	(95% CI)	(0.353, 0.438)	(0.191, 0.244)
	Secondary endpoints		
	Adjusted mean number of new or newly Enlarging T2 Hyperintense Lesions at Week 96	9.44	4.31
	(95% CI)	(8.46, 10.54)	(3.85, 4.81)
	Estimated proportion progressed (sustained increase in EDSS for 12 weeks) at week 96	0.143	0.120
	Estimated proportion of subjects relapse free at week 96	0.585	0.729
	% of patients with clinically meaningful worsening in MSIS-29 Physical Impact score	23	19
	Tertiary endpoint		
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 96	0.121	0.092

Effect estimate per comparison	Annualized relapse rate	Comparison groups	(% reduction Daclizumab 150 mg vs. IFN β-1a)
		ARR ratio	0,550
		95% CI	(0.469, 0.645)
		P-value	P<0.0001
	Adjusted mean number of new or newly Enlarging T2 Hyperintense Lesions at Weeks 96	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Lesion mean ratio	0.46
		95% CI	(0.39, 0.53)
		P-value	P<0.0001
	Estimated proportion progressed (sustained	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Hazard ratio*	0.84
		95% CI	(0.66, 1.07)

	increase in EDSS for 12 weeks)	P-value	P=0.1575
	Estimated proportion of subjects relapse free	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Hazard ratio*	0.59
		95% CI	(0.50, 0.69)
		P-value	P<0.0001
	% of patients with clinically meaningful worsening in MSIS-29 Physical Impact score	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Odds ratio	0.76
		95% CI	(0.60, 0.95)
		P-value	P= 0.0176
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks)	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Hazard ratio*	0.73
		95% CI	(0.55, 0.98)
		P-value	p=0.0332
Notes	* calculated over the treatment period up to 144 weeks.		

2.5.1.2.1. Study 205MS201

Methods

- **Treatments**

Subjects were randomized in a 1:1:1 ratio to receive 1 of the following doses:

- Group 1: placebo (3 SC injections every 4 weeks for a total of 13 doses)
- Group 2: 150 mg daclizumab (3 SC injections every 4 weeks for a total of 13 doses)
- Group 3: 300 mg daclizumab (3 SC injections every 4 weeks for a total of 13 doses)

Concomitant therapies

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue were not restricted, but were optimized as early as possible during screening in an attempt to maintain consistent treatment for the duration of the study.

Subjects were instructed not to start taking any new medications, including non-prescribed drugs, unless they received permission from the Investigator.

Disallowed therapies

Any alternative drug treatments directed towards the treatment of MS, such as chronic immunosuppressant therapy or other immunomodulatory treatments, with the exception of acute management of a protocol-defined relapse.

Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications. Any monoclonal antibodies other than daclizumab IV Ig, cladribine, plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination

Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined

treatment of relapses. Steroids that were administered by non-systemic routes (e.g., topical, inhaled) were allowed.

- **Objectives**

Primary objective

The primary objective of this study was to determine whether daclizumab, when compared to placebo, is effective in reducing the rate of relapses between baseline and Week 52. The primary endpoint was the change in annualized relapse rate between baseline and Week 52.

Secondary Objectives

The secondary objectives were to determine whether daclizumab is effective in:

- Reducing the number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects
- Reducing the number of new or newly enlarging T2 hyperintense lesions at Week 52
- Reducing the proportion of relapsing subjects between baseline and Week 52
- Improving quality of life as measured by the MSIS-29 physical score at Week 52 compared to baseline

Tertiary Objectives

There were a number of tertiary objectives including:

- slowing the progression of disability as measured 12 weeks, reduction in the number of new or newly enlarging T2 hyperintense lesions at Week 24 compared to baseline
- MRI: reduction of the number of Gd-enhancing lesions at Week 52 compared to baseline, reduction of the volume of new T1 hypointense lesions at Week 24 and Week 52 compared to baseline, reduction of the total lesion volume of new and newly enlarging T2 hyperintense lesions at Week 24 and Week 52 compared to baseline and at Week 52, reduction of the volume of non-Gd enhancing T1 hypointense ("blackholes") lesions at Week 24 and week 52 compared to baseline and at Week 52, efficacy in reducing brain atrophy on MRI at Week 24 over the 52-week treatment period, the efficacy of daclizumab in reducing the total lesion volume of T2 hyperintense lesions over the 52-week treatment period
- safety and tolerability
- time to relapse and disability progression from baseline to Week 52
- efficacy the subject's global impression of well-being as measured by a Visual Analogue Scale (VAS)
- efficacy on quality of life as measured by the MSIS-29 psychological scale, the SF-12, and the EQ-5D

- **Outcomes/endpoints**

Clinical Efficacy variables

Relapses

Definition of relapse

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. New or recurrent neurologic symptoms that evolved gradually over months

were considered disease progression, not an acute relapse. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

Evaluation of relapse cases by INEC

Independent Neurology Evaluation Committee (INEC): The INEC was established for the purpose of obtaining a consistent and independent blinded determination of whether a subject had experienced an MS relapse as defined by the protocol. The INEC included 5 members, all of whom were neurologists with expertise in MS.

Note: INEC-confirmed relapses were the primary way to define relapse in efficacy analyses. In sensitivity analyses of relapse outcomes, all relapses determined by the Investigator to meet the protocol definition of relapse were evaluated regardless of whether they were INEC-confirmed. In addition, all MS relapses as determined by the Investigator were captured as AEs of MS relapse and reported in safety tabulations regardless of whether they met the protocol definition of relapse or whether they were INEC-confirmed.

Disability Progression

Disability progression was assessed using the EDSS, an ordinal scale used to measure neurological impairment and disability [Kurtzke 1983]. Functional Scores (FS) scores were determined using the Neurostatus scoring worksheet and definitions (Version 12/05). The FS and the furthest distance the subject was able to walk without aid or rest were recorded along with the EDSS score on the CRF.

In this study, tentative EDSS progression was defined as a minimum change (i.e., at least a 1.0 point increase on the EDSS from baseline EDSS 1.0 or at least a 1.5 point increase on the EDSS from baseline EDSS = 0) that was present on a scheduled or unscheduled study visit. EDSS progression was considered confirmed when this minimum EDSS change was present on the next study visit occurring after 74 days from the initial observation.

Progression had to start prior to the end of the Week 52 treatment period but could have been confirmed either during the 205MS201 follow-up period or during the 205MS202 extension study. Progression was not confirmed at a visit where a relapse was also occurring.

MRI imaging

The MRI assessments were conducted at baseline (any time from screening to the baseline visit) and at Weeks 24, 36, and 52. In this MRI-intensive cohort (the first 307 subjects enrolled in the study), MRIs were also performed every 4 weeks between baseline and Week 24.

Professor Radue in Basel, Switzerland was selected by Biogen Idec to read and interpret all MRIs for this study.

DaclizumabPD Assessments

- Pharmacodynamic assessments
- The assessment of cell-mediated immunity using Cylex® Immunknow™ assay
- The assessment of CD25 expression on peripheral T cells (CD25 assay)
- Expanded lymphocyte phenotyping addressing T and cluster of differentiation (CD)56+ natural killer (NK) cells.
- Whole blood samples were collected and frozen for possible future ribonucleic acid (RNA) and DNA transcription profiling and genotyping, respectively

- Identification and/or analysis of serum biomarkers that may relate to daclizumab efficacy or MS disease activity such as soluble CD25 level. Serum collected for other assessments could have also been used for biomarker analysis.

• **Sample size**

It was assumed that if subjects were not allowed to add IFN-β during the study, the annualized relapse rate in the placebo group would be 0.50. However, because subjects were permitted to add IFN-β as a treatment for relapse, the annualized relapse rate in the placebo group would be reduced to 0.476 while the rate in the daclizumab group would stay the same. In this setting, a sample size of 198 subjects per treatment group would have approximately 90% power to detect a 50% reduction in the annualized relapse rate between a daclizumabtreatment group and placebo. Power was estimated from simulations assuming a negative binomial distribution, a 10% drop out rate, and a 5% type 1 error rate. Based on these assumptions, a sample size of 594 subjects would be required for the study.

• **Randomisation**

Subjects were randomized to receive daclizumab at doses of 150 mg or 300 mg every 4 weeks or placebo, with equal randomization (1:1:1) into each of the 3 treatment groups.

Randomization took place across all study sites using a centralized interactive voice response system (IVRS). The randomization was not stratified.

• **Blinding (masking)**

This study was double-blind. Treatment assignments were generated and assigned centrally through the IVRS system.

Except for the pharmacist (or designee) who was responsible for preparing the study treatment, all study staff and subjects were blinded to treatment. The Pharmacist did not have any interaction with the subjects and was strictly instructed not to communicate any information that could potentially unblind study personnel or the Sponsor to treatment assignment.

To further protect the blind during the study, a separate Treating Neurologist and Examining Neurologist were designated at each investigational site. The Treating Neurologist functioned as the primary treating physician during the study. The Examining Neurologist conducted all EDSS evaluations and relapse assessments but was not involved in any other aspect of subject care and was instructed to limit all interactions with subjects to the minimum necessary to perform the required neurologic examinations.

• **Statistical methods**

Analysis Populations

All analysis populations were defined and documented prior to database lock and were as follows:

Intent-to-treat (ITT) Population: The ITT population was defined as all randomized subjects who received at least 1 dose of study treatment. Subjects from 1 site (Site 903) were prospectively excluded from the ITT population after it was found that there was systematic misdosing by the unblinded pharmacist at the site. Subjects were analyzed according to the treatment to which they were randomized. Efficacy endpoints were evaluated using the ITT population. The efficacy analyses performed on the ITT population were considered the primary analyses.

Efficacy Evaluable Population: The efficacy-evaluable population was defined as all subjects in the ITT population who (1) had no missing MRI data from Weeks 8, 12, 16, 20, and 24 and (2) did not take prohibited alternative MS medications. MRI scans for these subjects were to be performed within $\pm$14

days of the target study day. The number of new Gd-enhancing lesions was evaluated using the efficacy evaluable population. The analyses based on the efficacy-evaluable population were considered supportive analyses.

Safety Population: The safety population included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline assessment of the safety parameter being analyzed. The safety population was used to analyze safety data.

Subjects Excluded From Analyses

Site 903 - was closed for misconduct and closure of Site 903 produced an ITT population of 196 subjects in the placebo group, 201 subjects in the Daclizumab 150 mg group, and 203 subjects in the Daclizumab 300 mg group. However, the 21 subjects excluded from the efficacy analyses were included in the safety analyses, and sensitivity analyses were performed to assess any effects their inclusion may have had on safety and efficacy analyses.

Efficacy analyses

Control of Type I Error Rate

Statistical testing for efficacy endpoints was performed between the Daclizumab 300 mg group and placebo and the Daclizumab 150 mg group and placebo separately. A sequential, closed testing procedure was used to control the overall type I error rate that might result from multiple comparisons. If the first comparison (300 mg versus placebo) was statistically significant ($p \leq 0.05$), then the second comparison (150 mg versus placebo) was tested at the $\alpha = 0.05$ significance level. However, if the first comparison was not statistically significant, then the second comparison was not considered statistically significant.

In order to control for a type I error for the secondary endpoints, the sequential closed testing procedure included both the order of the secondary endpoints and the order of testing of the dose groups. Specifically, for each of the secondary endpoints, a sequential closed testing procedure was used, with the first comparison (the Daclizumab 300 mg group versus placebo) and the second comparison (the Daclizumab 150 mg group versus placebo). Secondary endpoints were rank prioritized, in the following order:

1. The number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects
2. The number of new or newly enlarging T2 hyperintense lesions at Week 52
3. The proportion of relapsing subjects between baseline and Week 52
4. The change in MSIS-29 physical score at Week 52 compared to baseline

Tertiary supportive analyses did not include adjustments made for multiple comparisons and endpoints.

Model Characteristics

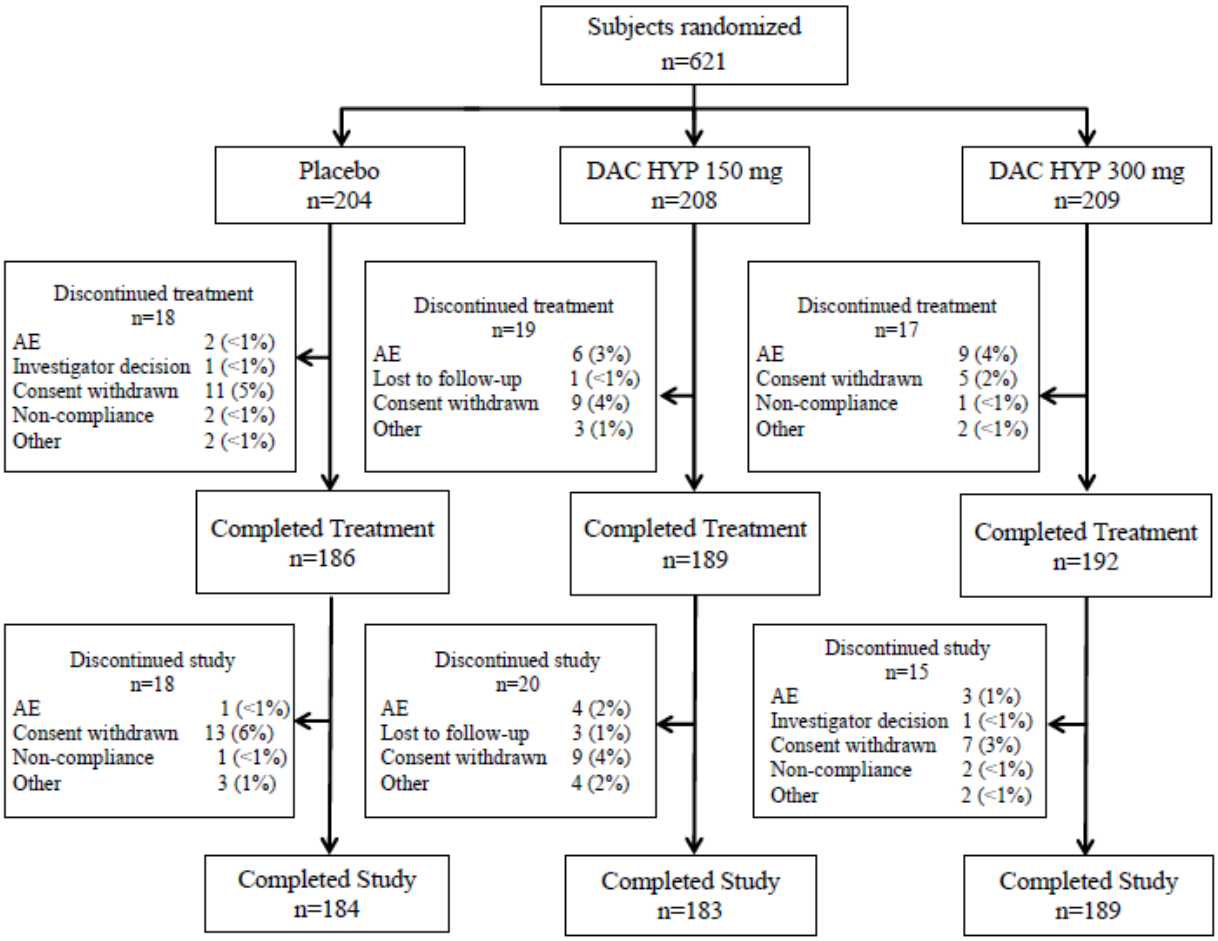
For the relapse endpoints (annualized relapse rate and proportion of relapsing subjects), the analysis models were adjusted for the number of relapses in the 1-year prior to study entry, baseline EDSS (EDSS 2.5 versus EDSS >2.5), and baseline age (age 35 versus age >35 years). For the disability progression endpoint, the model included a term for baseline EDSS (EDSS 2.5 versus EDSS >2.5) and baseline age (age 35 versus age >35 years). Other secondary and tertiary analyses included a term for treatment group and the baseline factor only.

All statistical tests were 2-sided with an overall Type I error rate of 0.05%.

RESULTS

- **Participant flow**

A total of 621 subjects (204 placebo; 208 Daclizumab 150 mg; 209 Daclizumab 300 mg) were randomized at 78 investigational sites in the Czech Republic, Germany, Hungary, India, Poland, Russia, Turkey, the Ukraine, and the United Kingdom. Evidence of deliberate misdosing was detected at 1 site during study monitoring, prompting the prospective exclusion of 21 subjects from the efficacy analysis prior to study completion, resulting in an ITT population of 196 subjects in the placebo group, 201 subjects in the Daclizumab 150 mg group, and 203 subjects in the Daclizumab 300 mg group. The 21 excluded subjects were included in the safety analysis.



Subjects who withdrew during the Study 201 follow-up period to enroll in the extension study were excluded from the total number of subjects who completed the study.
Source: CSR 205MS201, Table 14.

Figure 4 Study 205MS201- Subject Disposition

- **Recruitment**

The study started on 15 February 2008, with end of study date of 30 August 2011.

Clinical study report is dated 15 February 2013.

- **Conduct of the study**

The original protocol included one placebo group and three active groups, i.e. 25 mg, 100mg and 200mg. Doses of 150 mg and 300 mg were ultimately selected based on the fact that a minimum plasma concentration of 51 µg/ml would be need for the saturation of the CD25 receptor. Sample size was updated as a result.

- **Baseline data**

Demographic data

Table 13 Demographic data

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
Age (yrs)				
18-19	1 (<1)	4 (2)	5 (2)	10 (2)
20-29	46 (23)	55 (26)	53 (25)	154 (25)
30-39	79 (39)	73 (35)	90 (43)	242 (39)
40-49	60 (29)	67 (32)	49 (23)	176 (28)
50-55	18 (9)	9 (4)	12 (6)	39 (6)
n	204	208	209	621
Mean	36.6	35.3	35.2	35.7
SD	9.02	8.94	8.67	8.88
Median	37.0	36.0	35.0	35.0
Min, Max	19, 55	18, 54	18, 55	18, 55
Sex				
Female	128 (63)	140 (67)	134 (64)	402 (65)
Male	76 (37)	68 (33)	75 (36)	219 (35)
Race				
White	197 (97)	202 (97)	200 (96)	599 (96)
Asian	7 (3)	6 (3)	9 (4)	22 (4)
Black or African American	0	0	0	0
American Indian or Alaska native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	0	0	0	0
Height (cm)				
n	204	207	209	620
Mean	169.54	169.93	169.33	169.60
SD	9.424	9.805	9.879	9.694
Median	169.00	168.00	168.00	168.00
Min, Max	140.0, 202.0	149.0, 198.0	150.0, 196.0	140.0, 202.0

Weight (kg)				
n	203	207	209	619
Mean	69.99	68.31	68.20	68.82
SD	14.443	15.878	15.195	15.185
Median	68.00	64.00	66.50	66.30
Min, Max	40.0, 141.0	38.2, 130.0	33.0, 118.0	33.0, 141.0
Body mass index (kg/m^2)				
n	203	207	209	619
Mean	24.30	23.53	23.63	23.82
SD	4.566	4.474	4.129	4.398
Median	23.57	22.79	23.01	23.05
Min, Max	17.3, 52.4	15.7, 40.3	13.1, 39.9	13.1, 52.4
Body surface area (m^2)				
n	203	207	209	619
Mean	1.81	1.79	1.78	1.79
SD	0.212	0.239	0.235	0.229
Median	1.78	1.73	1.77	1.76
Min, Max	1.3, 2.5	1.3, 2.7	1.2, 2.4	1.2, 2.7

NOTE: Numbers in parentheses are percentages.

SOURCE: DACMS/205MS201/CSR/T-DM-DEMOG.SAS DATE: 27DEC2011

According to the data patients had 2.4 relapses in the past 3 years, with 1.4 relapses in the past 12 months alone and with a time lapse of 5.5 months on average since the last relapse.

The maximum EDSS score at entry into the study was 5. Patients presented with a mean EDSS score of 2.7, which complies with the characteristics for most patients enrolled in clinical trials for MS. Most patients presented with McDonald criterion 1, i.e. 2 or more relapses and 2 or more objective lesions. It should be noted that patients in the low daclizumab group had a slightly higher median EDSS score (3.0 instead of 2.5 in the other groups).

Baseline MRI (main)

Patients had a mean number of T2 lesions of 39.5, 44.6 and 35.9 respectively in the placebo, 150 mg Daclizumab and 300 mg Daclizumab. The difference between the two daclizumab groups is important, corresponding to a 40% increase in volume.

The mean volume of T1 hypointense lesions was largely comparable between pplacebo and active, with 2238.0, 2738.4 and 2030.5 mm3 in the placebo, the 150mg Daclizumab and the 300mg Daclizumab groups respectively. The difference between the two active groups is nevertheless notable.

The number of Gd-enhancing lesions was similar between the placebo and the Daclizumab 150mg (2.0 and 2.1 respectively) but was only 1.4 in the 300 mg Daclizumab group.

There was no notable difference between groups for the normalised brain volume.

Altogether the 300mg Daclizumab group presented with a lesser burden of T2 lesions accompanied by a lesser volume of T1 hypointense lesions as compared to placebo and especially to the 150 mg Daclizumab group.

Prior MS therapy

Table 14 Prior use of approved MS therapy

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
Number of subjects with prior use of approved RRMS treatments	26 (13)	41 (20)	31 (15)	98 (16)
INTERFERON BETA-1B	8 (4)	20 (10)	16 (8)	44 (7)
INTERFERON BETA-1A	10 (5)	15 (7)	11 (5)	36 (6)
GLATIRAMER	8 (4)	9 (4)	9 (4)	26 (4)
NATALIZUMAB	0	2 (<1)	0	2 (<1)
MITOXANTRONE	1 (<1)	0	0	1 (<1)

NOTE 1: Numbers in parentheses are percentages.
2: Prior use of approved RRMS treatments INTERFERON BETA-1A, INTERFERON BETA-1B, NATALIZUMAB, GLATIRAMER and MITOXANTRONE were included in this table.

SOURCE: DACMS/205MS201/CSR/T-CM-PREVMS-EXCL-CORT1.SAS DATE: 09AUG2012

20% of patients in the in the 150mg Daclizumab group had prior treatment for MS (mainly Interferon) as compared to 13% in the placebo group and 15% in the 300mg group.

Concomitant medication

Concomitant medication during Study 205MS201 was similar between groups with a higher frequency of patients receiving methylprednisolone in the placebo group; time on treatment was comparable between groups.

To note IFN-β was taken as a protocol-allowed concomitant medication after Month 6 in subjects experiencing a relapse by 7 subjects in the study (5 in the placebo group and 1 each in the Daclizumab 150 mg and Daclizumab 300 mg groups).

- **Numbers analysed**

ITT population**:** The ITT population includes all randomized subjects who received at least 1 dose of study medication, excluding 21 subjects from Site 903. Subjects were analyzed according to the treatment group to which they were randomized (196 subjects in the placebo group, 201 subjects in the Daclizumab150 mg group, and 203 subjects in the Daclizumab 300 mg group).

Efficacy-evaluable population**:** The efficacy-evaluable population includes subjects in the ITT population with non-missing MRI data from Weeks 8, 12, 16, 20, and 24 who did not take prohibited alternative MS medications during the treatment period and who had their baseline MRI scan prior to their first dose of study treatment.

Subjects must have had their MRI scans carried out within 14 days of the target study day as indicated on the study activities chart.

- **Outcomes and estimation**

Primary efficacy endpoint analysis

The primary analysis of the annualized relapse rate was based on INEC-confirmed relapses and it included data from all subjects in the ITT population until either the end of the treatment period, a switch to alternative MS medication, or withdrawal from the study. Treatment group differences were compared

using a negative binomial regression model adjusted for the number of relapses in the 1 year prior to study entry, baseline EDSS (2.5 vs. >2.5), and age (35 vs. >35 years).

The adjusted annualized relapse rate in the placebo group was 0.458 [95% CI: 0.370, 0.566], compared to 0.211 [95% CI: 0.155, 0.287] in the Daclizumab 150 mg group and 0.230 [95% CI: 0.172, 0.308] in the Daclizumab 300 mg group. The annualized relapse rate ratio was 0.461 (95% CI: 0.318, 0.668) for Daclizumab 150 mg versus placebo and 0.503 (95% CI: 0.352, 0.721) for Daclizumab 300 mg versus placebo, indicating that the annualized relapse rate was reduced by 54% in the Daclizumab 150 mg group ($p<0.0001$) and by 50% ($p = 0.0002$) in the Daclizumab 300 mg group, compared with placebo (Table 15).

Table 15 Primary analysis - Annualized Relapse Rate between Baseline and Week 52 - Negative Binomial Regression

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Number of relapses			
0	127 (65)	163 (81)	163 (80)
1	52 (27)	33 (16)	34 (17)
2	15 (8)	5 (2)	5 (2)
3	2 (1)	0	1 (<1)
>= 4	0	0	0
Total number of relapses	88	43	47
Total subject-years followed	190.39	193.90	197.51
Unadjusted annualized relapse rate (a)	0.462	0.222	0.238
Adjusted relapse rate (95% CI) (b)	0.458 (0.370,0.566)	0.211 (0.155,0.287)	0.230 (0.172,0.308)
Rate ratio (95% CI)(b)		0.461 (0.318,0.668)	0.503 (0.352,0.721)
p-value vs placebo		<0.0001	0.0002
Subject relapse rate (c)			
n	196	201	203
Mean	0.484	0.229	0.250
SD	0.7958	0.5419	0.6024
Median	0.000	0.000	0.000
25th, 75th percentile	0.000, 1.001	0.000, 0.000	0.000, 0.000
Min, Max	0.00, 4.96	0.00, 4.20	0.00, 4.94

Note 1: Numbers in parentheses are percentages.
2: Data after subjects switched to alternative MS medications are excluded.
(a) Total number of relapses that occurred during the study divided by the total number of subject-years followed in the study.
(b) Estimated from a negative binomial regression model adjusted for the number of relapses in the 1 year prior to study entry (p= 0.005), baseline EDSS (<= 2.5 vs > 2.5, p= 0.411), and age (<= 35 vs > 35, p= 0.063).
(c) Number of relapses for each subject divided by the number of years followed in the study for that subject. Summary statistics are presented.

SOURCE: DACMS/205MS201/CSR/T-ARR-BS-NB.SAS DATE: 27DEC2011

The primary endpoint has been met for both dose groups. The benefit seemed similar in the two dose groups, with a 50% reduction in relapse rates in the 300mg group (as evidenced by the rate ratio of 0.50) and a 54% reduction in the 150mg group (from the 0.46 rate ratio). Both results were highly statistically significant, with the upper bound of the confidence interval for the rate ratio being well below 1.00.

Even without formal statistical analysis the benefit is clear, with approximately twice as many relapses in the placebo group compared to both active groups, the number of patients reporting 0 relapses about

15% higher in the active groups compared to placebo, and the placebo group having more patients in all of the 1, 2 and 3 relapse categories.

Sensitivity analyses

Multiple sensitivity analyses were performed to assess the robustness of the primary analysis. Alterations were made to the regression model parameters used to assess treatment effects on the annualized relapse rate:

b) using a Poisson regression model instead of a negative binomial regression model

c) excluding time and relapses that occurred after stopping study treatment (c)

d) including time on study and relapses that occurred after starting alternative MS medications

e) excluding relapses and follow-up time that occurred after starting protocol allowed concomitant use of IFN-

f) adjusting the analysis only for the number of relapses in the 1 year prior to study entry

g) including all relapses that met the protocol-defined objective relapse criteria (INEC confirmed or not)

h) including the 21 subjects from Site 903 who had been prospectively excluded from the ITT population

The results of these sensitivity analyses were all supportive and similar to the primary analysis presented above, indicating that the primary result was robust to a range of factors, including modelling assumptions, use of concomitant therapies that can affect annualized relapse rate, and the exclusion of subjects from 1 site from the ITT population.

Subgroup analyses

Predefined subgroups were evaluated for the primary efficacy endpoint (annualized relapse rate). The predefined subgroups included the following and the Daclizumab 150 and Daclizumab300 were combined:

- gender (male vs. female)
- age (>35 vs. ≤ 35 years)
- weight (≥ median vs. < median)
- number of relapses in the past 12 months (≤ 1 vs. >1)
- baseline EDSS (>2.5 vs. ≤ 2.5)
- baseline Gd lesions (present vs. absent)
- baseline CD25 (≥ median vs. < median)
- soluble CD25 (≥ median vs. < median)
- CD25 SNP rs2104286 (CC+TC vs. TT)

In addition as a post-hoc analysis:

- subjects who received prior MS medication (yes vs. no)
- disease activity at baseline (high vs. low)

High disease activity at baseline was defined as ≥ 2 relapses in year prior to randomization and ≥ 1 Gd-enhancing lesion at baseline.

Subgroup analyses demonstrated that daclizumab was effective across all demographic and baseline characteristic subgroups. While there was minor variation in treatment effect estimates across the multiple subgroups analyzed, some subgroups involved small numbers of patients and results appeared consistent with sampling variability. Subgroups for which point estimates of daclizumab treatment effect were stronger for the annualized relapse rate endpoint did not show concordant findings when using the MRI endpoints, and overall there was no convincing evidence for effect modification by any of the characteristics analysed.

Secondary Endpoints

1. Number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects

The adjusted mean numbers of new lesions from Weeks 8 to 24 after adjustment were 4.79 lesions for placebo, 1.46 lesions for Daclizumab 150 mg, and 1.03 lesions for Daclizumab 300 mg. This result indicated that treatment with Daclizumab 150 mg and 300 mg reduced the number of new Gd-enhancing lesions between Weeks 8 and 24 after initiation of treatment by 69% ($p<0.0001$) and 78.4% ($p<0.0001$), respectively.

When the data for new Gd-enhancing lesions were analyzed by visit in the MRI-intensive population, the number of Gd-enhancing lesions in both daclizumab dose groups was significantly lower than that in the placebo group at all post-treatment time points beginning at the Week 4 MRI after adjustment for the baseline number of Gd+ lesions. This effect over time was also evident in the ITT population when examining new Gd-enhancing lesions at Weeks 24, 36, and 52.

Table 16 Number of New Gd-Enhancing Lesions between Week 8 and Week 24 - MRI Intensive Population – Primary Analysis

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in MRI intensive population	105	101	103
Number of subjects in MRI intensive population in the analysis (a)	104 (100)	101 (100)	102 (100)
Number of new Gd-enhancing lesions			
n	104	101	102
Mean	5.7	3.1	1.4
SD	9.98	9.21	2.99
Median	2.0	0.0	0.0
Min, Max	0, 78	0, 67	0, 17
0	29 (28)	54 (53)	70 (69)
1	18 (17)	16 (16)	12 (12)
2	9 (9)	8 (8)	2 (2)
3	6 (6)	5 (5)	3 (3)
>=4	42 (40)	18 (18)	15 (15)
Adjusted mean number of new Gd lesions (b)	4.79	1.46	1.03
95% CI (b)	3.56, 6.43	1.05, 2.03	0.73, 1.46
Percent reduction (b)		69.47	78.44
95% CI (b)		52.40, 80.41	65.97, 86.35
p-value vs placebo		<0.0001	<0.0001

NOTE 1: Numbers in parentheses are percentages.
2: For subjects with missing data the last valid non baseline measurement was carried forward if the subject was missing only 1 or 2 consecutive post-baseline scans. Otherwise the mean based on treatment group and visit was used as the imputed value.
(a) Number of subjects in MRI intensive populations with non-missing baseline values
(b) Estimated from a negative binomial model adjusted for the baseline number of Gd-enhancing lesions.

SOURCE: DACMS/205MS201/CSR/T-GD824-ITT.SAS DATE: 27DEC2011

Multiple sensitivity analyses were performed to evaluate the robustness of the primary analysis. In 2 sensitivity analyses, modifications were made to the analysis population: a) analysis restricted to the efficacy-evaluable population; b) MRI-intensive population excluding subjects who did not receive all assigned study doses. In 2 sensitivity analyses, modifications were made to the MRI scans that were eligible for inclusion in the analysis: analysis including the Week 4 MRI scan (new Gd-enhancing lesions between Weeks 4-24) and c) analysis excluding any MRI scans taken within 24 days of steroid treatment. One additional sensitivity analysis was performed to assess the statistical model and effect of outliers: d) analysis with new lesion number truncated at 30.

The results of these sensitivity analyses were all supportive and similar to the primary analysis.

2. Number of new or newly enlarging T2 hyperintense lesions at Week 52

The number of new or newly enlarging T2 hyperintense lesions at Week 52 was evaluated using the baseline MRI scan as a reference. Treatment effects on the number of new T2 lesions at Week 52 were analyzed using a negative binomial regression model adjusting for the baseline number of T2 lesions.

The adjusted mean number of new or newly enlarging T2 hyperintense lesions at Week 52 was 8.13 (95% CI: 6.65, 9.94) in the placebo group, 2.42 (95% CI: 1.96, 2.99; p<0.0001) in the Daclizumab 150 mg group, and 1.73 (95% CI: 1.39, 2.15; p<0.0001) in the Daclizumab 300 mg group. This result indicated

that Daclizumab150 mg reduced the number of new or newly enlarging T2 lesions by 70% (p<0.0001) and Daclizumab 300 mg reduced it by 79% (p<0.0001), respectively compared to placebo.

In the placebo group, 19% of subjects had no new or newly enlarging T2 lesions at Week 52 compared to 46% in the Daclizumab 150 mg group and 52% in the Daclizumab 300 mg group.

Table 17 Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196	201	203
Number of subjects in ITT population in the analysis (a)	195 (100)	199 (100)	200 (100)
Number of new or newly enlarging T2 hyperintense lesions at 52 weeks			
n	195	199	200
Mean	8.2	3.4	2.1
SD	9.34	8.15	5.19
Median	6.0	1.0	0.0
Min, Max	0, 56	0, 86	0, 53
0	38 (19)	91 (46)	104 (52)
1	16 (8)	25 (13)	24 (12)
2	14 (7)	15 (8)	35 (18)
3	9 (5)	27 (14)	8 (4)
>=4	118 (61)	41 (21)	29 (15)
Adjusted mean number of new or newly enlarging T2 hyperintense lesions	8.13	2.42	1.73
95% CI (b)	6.65, 9.94	1.96, 2.99	1.39, 2.15
Percent reduction (b)		70.23	78.73
95% CI (b)		59.94, 77.88	71.33, 84.22
p-value vs placebo (c)		<0.0001	<0.0001

NOTE 1: Number in parentheses are percentages.
2: Missing data is imputed using the mean within each treatment group.
(a) Number of subjects in ITT population with a non-missing baseline value.
(b) Estimated from a negative binomial model adjusted for the baseline number of T2 lesions.
(c) P-value for comparison between the treated and placebo groups based on negative binomial regression adjusted for baseline number of T2 lesions.

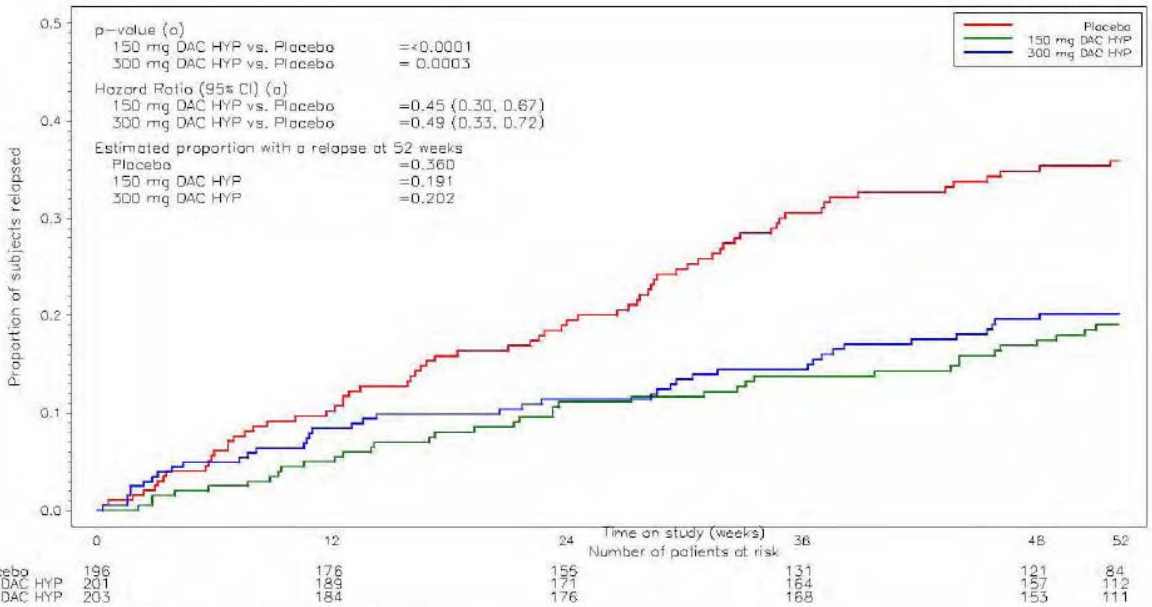
3. Proportion of relapsing subjects between baseline and Week 52

The Kaplan-Meier estimate for the proportion of subjects who relapsed at Week 52 was 36% in the placebo group compared to 19% in the Daclizumab150 mg and 20% in the Daclizumab300 mg group. The hazard ratio was 0.45 (95% CI: 0.30, 0.67) in the Daclizumab150 mg group compared to placebo and 0.49 (95% CI: 0.33, 0.72) in the DAC 300 mg group compared to placebo. These results indicate that the proportion of relapsing subjects was reduced by 55% in the Daclizumab 150 mg group (p<0.0001) and 51% (p = 0.0003) in the Daclizumab 300 mg group, compared to placebo.

Table 18 Proportion of Relapsing Subjects between Baseline and Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196	201	203
Subject status at 52 weeks			
Relapsed	69 (35)	38 (19)	40 (20)
Censored	127 (65)	163 (81)	163 (80)
Reason for censoring			
Completed treatment period	118 (60)	152 (76)	153 (75)
Early withdrawal from study	8 (4)	11 (5)	10 (5)
Alternative MS medication	1 (<1)	0	0
Estimated cumulative proportion of subjects relapsed at (a)			
12 weeks	0.10	0.05	0.08
24 weeks	0.20	0.11	0.11
36 weeks	0.31	0.14	0.14
48 weeks	0.35	0.17	0.20
52 weeks	0.36	0.19	0.20
Time (wk) relapse (a)			
10th percentile	11.7	23.3	20.6
25th percentile	30.1	NA	NA
50th percentile (Median)	NA	NA	NA
Hazard Ratio and 95% CI (b)		0.45 (0.30-0.67)	0.49 (0.33-0.72)
p-value vs placebo (b)		<0.0001	0.0003

NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored.
(a) Based on the Kaplan-Meier product limit method.
(b) Estimated from the Cox proportional hazards model. Covariates included were number of relapses in the 1 year prior to study entry (p=0.001), baseline EDSS (<=2.5 versus >2.5, p=0.449), and age (<=35 versus >35, p=0.026).



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored.
(a) P-value and hazard ratio are based on Cox proportional hazards model, adjusted for number of relapses in the 1 year prior to study entry, baseline EDSS (<=2.5 vs. >2.5), and age (<=35 vs. >35).

Figure 5 Time to first relapse (INEC confirmed relapses)

4. Change in MSIS-29 physical score at Week 52

The analysis of this endpoint demonstrated a nominally statistically significant benefit in the Daclizumab 150 mg group compared to placebo but not in the Daclizumab 300 mg group. The mean ± SD change in the MSIS-29 physical score from baseline to Week 52 was 3.0 ± 13.52 in the placebo group, - 1.0 ± 11.80 in the Daclizumab 150 mg group (p = 0.0008 vs. placebo), and 1.4 ± 13.53% in the Daclizumab 300 mg group (p = 0.1284 vs. placebo). The difference for Daclizumab 150 mg versus placebo was not considered statistically significant per the sequential closed testing procedure because the procedure required that the 300 mg dose group be tested first and achieve statistical significance before the 150 mg dose group could be tested.

Table 19 Change in MSIS-29 Physical Score at Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Change from Week 0 to Week 52			
n	196	201	203
Mean	3.0	-1.0	1.4
SD	13.52	11.80	13.53
Median	2.5	0.0	0.0
Min, Max	-56, 65	-39, 38	-43, 47
p-value vs placebo (a)		0.0008	0.1284
Relative mean change (95% CI) (a)		-4.27 (-6.76,-1.78)	-1.93 (-4.42,0.56)

NOTE: If the subject is missing data for less than 10 of the 20 items that make up the physical score, the mean of the non-missing items will be used for the missing items. If the subject is missing data for 10 or more items, the score was imputed using a mixed effects model (including visit week, treatment group, and their interaction, with random intercept and slope for each subject).
(a) Analysis of variance for difference between treatment groups, controlling for baseline score.

Tertiary Endpoints

- Disability progression

The risk of 12-week sustained disability progression at 52 weeks as measured by increase on the EDSS was reduced in the Daclizumab 150 mg group by 57% (hazard ratio (HR) = 0.43; 95% CI, 0.21 to 0.88; p = 0.0211) and in the Daclizumab 300 mg group by 43% (hazard ratio = 0.57; 95% CI, 0.30 to 1.09; p = 0.0905).

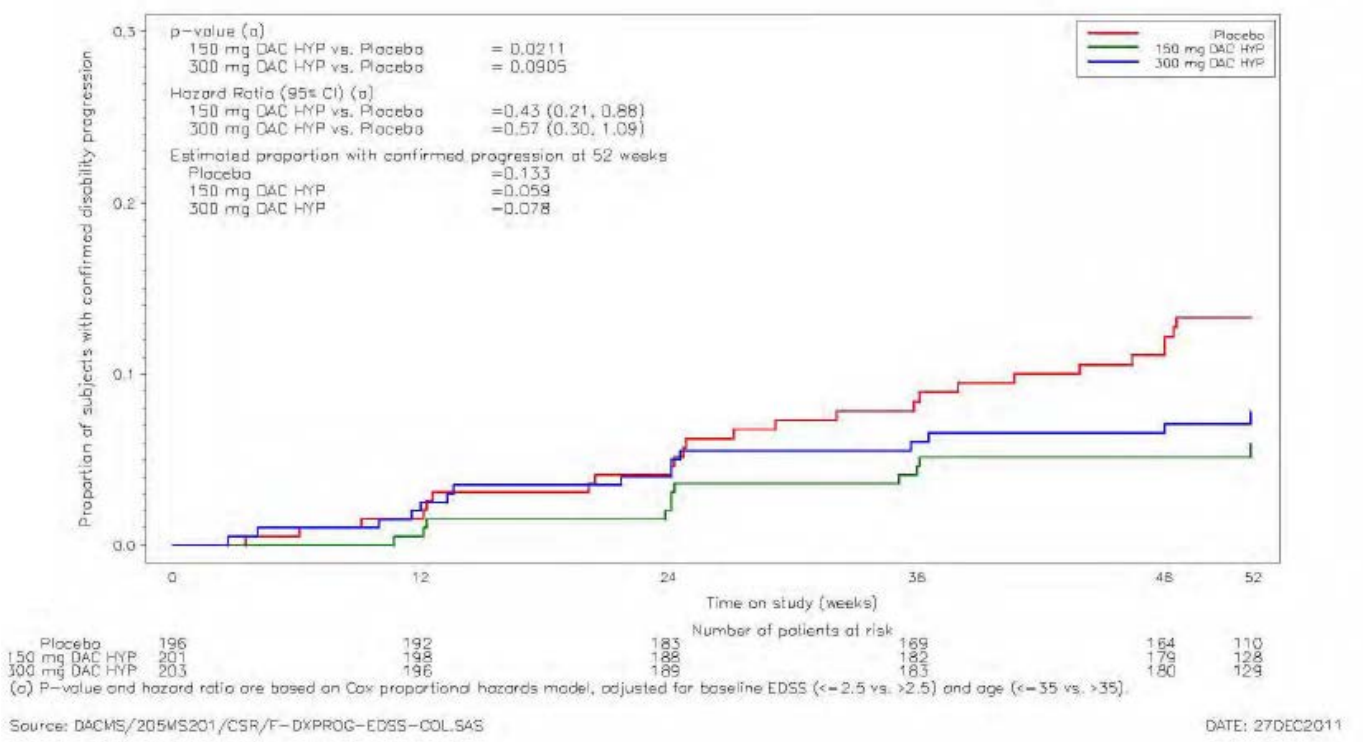


Figure 6 Time to Sustained Progression of Disability as Measured by Increase in EDSS

As in the protocol-defined analysis, the risk of 24-week sustained disability progression on EDSS was significantly reduced in the Daclizumab 150 mg group (p = 0.0037) but not in the Daclizumab 300 mg group (p = 0.1487) compared with placebo. The hazard ratios relative to placebo were 0.24 (95% CI: 0.09, 0.63) for Daclizumab 150 mg and 0.60 (95% CI: 0.30, 1.20) for Daclizumab 300 mg.

Table 20 Summary of time to 24 –week sustained progression of disability measured by increase in EDSS

Summary of time to 24-week sustained progression of disability measured by increase in EDSS

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Number of subjects who progressed	21 (11)	5 (2)	13 (6)
Time (wk) to progression (a)			
25th percentile	NA	NA	NA
50th percentile	NA	NA	NA
Estimated proportion of subjects with progression at 52 weeks (a)	0.111	0.026	0.068
Hazard ratio and 95% CI (b)		0.24 (0.09-0.63)	0.60 (0.30-1.20)
p-value vs placebo (b)		0.0037	0.1487

NOTE: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 24 weeks.
(a) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.
(b) Hazard ratio and p-value assessing the difference between the treatment groups were estimated from a Cox proportional hazards model. Covariates included were baseline EDSS (<=2.5 versus >2.5, p= 0.037), and age (<=35 versus >35, p= 0.047).

SOURCE: DACMS/205MS201/CSR/T-DXPROG-EDSS-24WK.SAS DATE: 12DEC2012

2.5.1.2.2. Study 205MS301

Methods

- **Treatments**

All subjects received study treatment (either daclizumab or Avonex or their respective matching placebos) starting at Week 0 (Baseline Visit) and ending at Week 144 or when the last subject enrolled had completed the Week 96 Visit, whichever was sooner.

- Subjects randomized to Group 1 received an injection of Daclizumab 150 mg SC once every 4 weeks plus A-PLC IM once weekly for 96 to 144 weeks.
- Subjects randomized to Group 2 received IFN β-1a 30 µg IM once weekly plus D-PLC SC once every 4 weeks for 96 to 144 weeks.

Treatment of relapses

Subjects who experienced a suspected MS relapse could be treated with intravenous methylprednisone (IVMP) 1000 mg/day for 3 to 5 days. Methylprednisolone could be given once a day or in divided doses.

Objectives

Primary Objective

The primary study objective was to test the superiority of daclizumab compared with IFN β-1a in preventing MS relapse in subjects with RRMS.

Secondary Objectives

The secondary study objectives were to test the superiority of daclizumab compared with IFN β-1a in slowing functional decline and disability progression and maintaining quality of life in this subject population.

Additional/Exploratory Objectives

Additional objectives of this study were to monitor the safety and tolerability of daclizumab; to measure DAC HYP trough levels; to monitor immunogenicity; to determine the efficacy of daclizumabversus IFN β-1a in slowing cognitive, visual, and physical decline and reducing brain atrophy; and to evaluate pharmacodynamic (PD) parameters that may be associated with treatment response in this subject population.

- **Outcomes/endpoints**

Primary endpoint

The primary endpoint was the annualized relapse Rate (ARR).

Secondary endpoints (ranked ordered)

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks
- Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 that was sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks
- Proportion of subjects who were relapse free

- Proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact

Tertiary endpoints

- Safety and tolerability as measured by physical and neurological examinations, vital signs, clinical laboratory assessments (hematology, blood chemistry, thyroid function panel [thyroid-stimulating hormone (TSH) and thyroxine (T4)], urinalysis), electrocardiograms (ECGs), Beck Depression Inventory, Second Edition (BDI-II), drug trough levels and immunogenicity assessments, injection site assessments, and AE and concomitant medication monitoring
- Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from a baseline EDSS ≥1.0 that was sustained for 24 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 24 weeks
- Visual function as measured by the visual function test (VFT)
- Change in Multiple Sclerosis Functional Composite (MSFC) score
- Change in Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), and 3-Second Paced Auditory Serial Addition Test (PASAT 3) scores
- Change in oral Symbol Digit Modalities Test (SDMT)
- Change in EDSS score
- Proportion of subjects who are free of disease activity
- Change in quality of life on the European Quality of Life, 5 dimensions (EQ-5D and EQ-VAS), MSIS-29 Psychological Impact score, and MSIS-29 Physical Impact score
- Brain atrophy
- Total number and volume of new T1 hypointense lesions, T2 hyperintense lesions, and Gd+ lesions on brain MRI scans
- Change in CD56bright NK cells, CD4+ T cells, and Fox P3+ regulatory T cells
- Healthcare Resource Utilization (HRU)

Sample size

A sample size of 900 subjects per treatment group would have approximately 90% power to detect a 24% reduction in the ARR between the IFN β-1a treatment group and the daclizumab treatment group based on a negative binomial regression model with a 5% type 1 error rate. Power was estimated from simulations assuming a 21% drop-out rate, an average of 2.4 years of follow-up, and an ARR of 0.27 in the IFN β-1a group. Approximately 1800 subjects were required for this study. The actual number of subjects randomised (1841) was in line with the planned sample size of 1800.

Randomisation

Subjects were randomized to receive either Daclizumab 150 mg SC once every 4 weeks plus A-PLC IM once weekly or IFN β-1a 30 μg IM once weekly plus D-PLC SC once every 4 weeks in a 1:1 ratio.

Randomization took place using a centralized centralized interactive voice response system (IVRS). Randomization was stratified by site and prior use of IFN-β using permuted block randomization.

- **Blinding (masking)**

This study was double-blind. Treatment assignments were generated and assigned centrally through the IVRS system. No code-breaking supplies to break the blind were provided to the study sites.

Statistical methods

Analysis Populations

All analysis populations were defined and documented prior to database lock and were as follows:

Intent-to-treat (ITT) Population: The ITT population included all randomized subjects who received at least 1 dose of any study treatment. Subjects were analyzed in the group to which they were randomized. In general, efficacy endpoints were analyzed using the ITT population as the primary analysis, although subjects with missing data for baseline covariates were excluded.

The main analysis of the number of new or newly enlarging T2 lesions at Week 96 was evaluated in the subset of subjects with non-missing post baseline scan data; sensitivity analyses of this endpoint included all subjects.

Per-protocol population: The per-protocol population was defined as subjects from the ITT population who satisfied the following conditions:

- Met both inclusion criteria related to MS-specific disease activity:
    - Had a confirmed diagnosis of RRMS according to McDonald criteria 1-4 and a cranial MRI demonstrating lesion(s) consistent with MS.
    - Had a baseline EDSS between 0.0 and 5.0, inclusive.
- Compliant with study treatment: $\geq$ 90% of daclizumab or Avonex doses up to Week 96.
- Did not permanently discontinue study treatment prior to Week 96.

The primary and secondary endpoints were evaluated on the per-protocol population as supportive analyses.

Safety Population: The safety population was defined as all subjects who received at least 1 dose of any study treatment. All safety analyses were based on the safety population.

Subjects Excluded From Analyses

There were no centres or subjects excluded from the analysis.

Efficacy analyses

Control of Type I Error Rate

Statistical testing for efficacy endpoints was performed between the Daclizumab 150 mg group and the Avonex (IFN β-1a) 30 μg group. The secondary endpoints are listed in the order of importance. In order to control for inflation of type I error due to multiple treatment comparisons for the secondary endpoints, a sequential closed testing procedure was employed with the sequence of endpoints defined as follows:

The secondary endpoints (rank ordered) for this study were:

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks

- Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 that was sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks
- Proportion of subjects who were relapse free
- Proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks

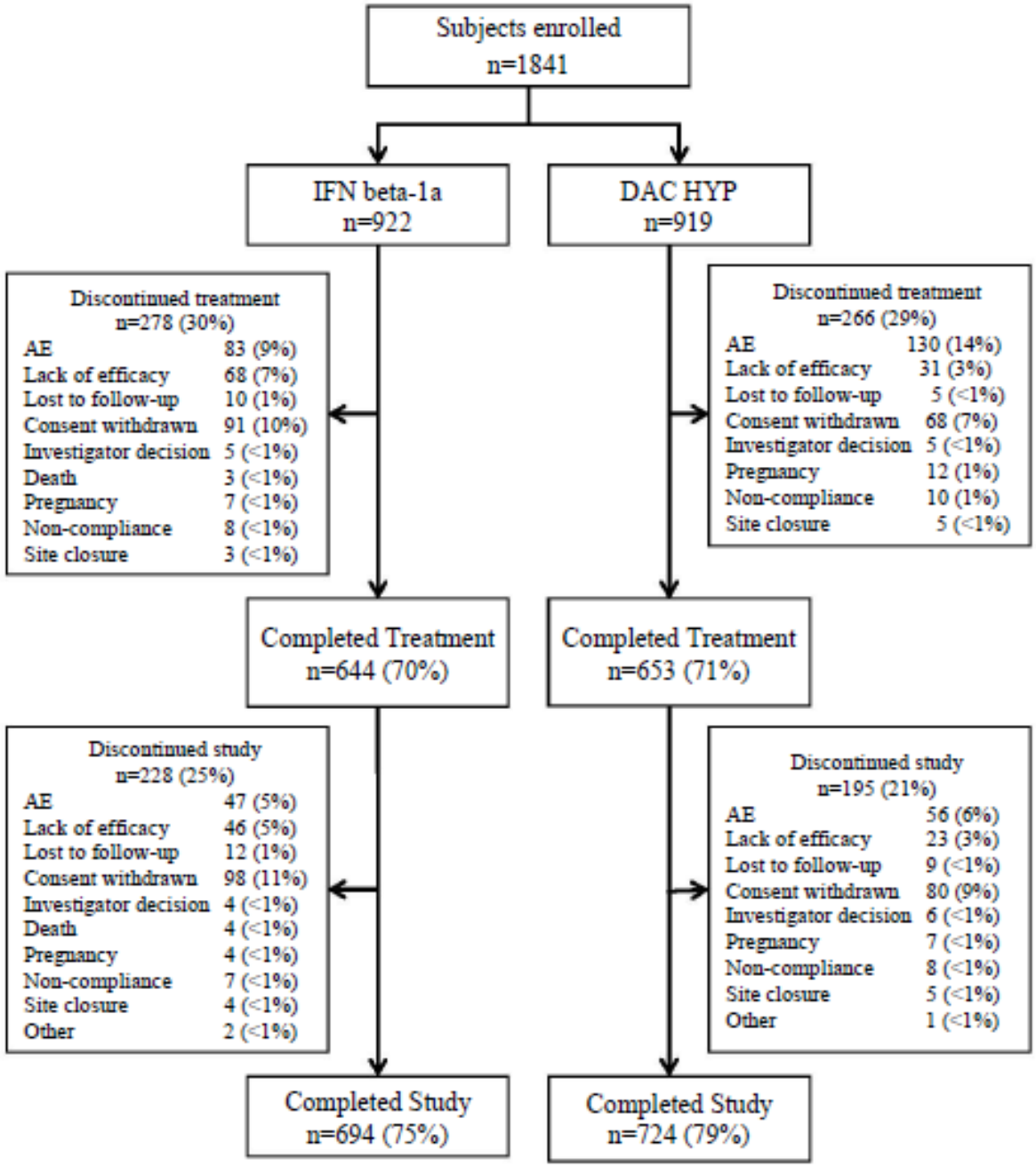
If the first comparison (number of new or newly enlarging T2 hyperintense lesions over 96 weeks) was statistically significant ($p<0.05$), the second comparison (disability progression) was then tested at the 0.05 significance level. However, if the first (or any subsequent) comparison was not statistically significant, then all endpoint(s) of a lower rank were not considered statistically significant.

Tertiary supportive analyses did not include adjustments made for the multiple comparisons for endpoints.

Results

- **Participant flow**

A total of 1841 subjects were randomized to treatment at 246 investigational sites in 28 countries worldwide. All 1841 subjects randomized received at least 1 dose of study treatment. The highest enrolling countries were Poland (451 subjects), United States (217 subjects), Russian Federation (198 subjects), Ukraine (129 subjects), and Serbia (111 subjects). All other countries each enrolled fewer than 100 subjects.



Source: Table 17.

Figure 7 Study 301 - Subject Disposition

Outcomes and estimation

1. **Primary efficacy endpoint analysis**

The primary analysis of the annualized relapse rate was based on INEC-confirmed relapses and it included data from all subjects in the ITT population between the first dosing date and the subject's end of treatment period visit or a switch to alternative MS medication. Treatment group differences were compared using a negative binomial regression model adjusted for the baseline relapse rate (number of relapses in the 3 years prior to study entry divided by 3), history of prior IFN β-1a use, baseline EDSS score (≤2.5 vs. >2.5), and age (≤35 vs. >35 years).

In the primary analysis, the adjusted ARRs were 0.393 (95% CI: 0.353, 0.438) in the IFN β-1a treatment group and 0.216 (95% CI: 0.191, 0.244) in the daclizumab treatment group. The adjusted ARR ratio (daclizumab/IFN β-1a) was 0.550 (95% CI: 0.469, 0.645), indicating that daclizumab reduced the ARR by 45% (95% CI: 35, 53%) compared with IFN β-1a (p <0.0001).

Table 21 Primary analysis: Annualised relapse rate

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects with a relapse	392 (43)	260 (28)
Number of relapses per subject		
0	530 (57)	659 (72)
1	227 (25)	174 (19)
2	109 (12)	51 (6)
3	36 (4)	20 (2)
>= 4	20 (2)	15 (2)
Total number of relapses	643	402
Total number of subject-years followed	1822.92	1897.57
Unadjusted annualized relapse rate (a)	0.353	0.212
Adjusted annualized relapse rate (95% CI) (b)	0.393 (0.353, 0.438)	0.216 (0.191, 0.244)
Rate ratio (DAC HYP/IFN beta-1a) (95% CI) (b)		0.550 (0.469, 0.645)
p-value vs IFN beta-1a (b)		<0.0001
Subject relapse rate (c)		
n	922	919
Mean	0.50	0.32
SD	1.110	2.467
Median	0.00	0.00
Min, Max	0.0, 12.6	0.0, 73.1

NOTE 1: Only relapses confirmed by INEC are included in this analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.
(a) Total number of relapses that occurred during the study divided by the total number of subject-years followed in the study.
(b) Estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (<=2.5 vs >2.5) and baseline age (<=35 vs >35).
(c) Number of relapses for each subject divided by the number of years followed in the study for that subject. Summary statistics across all subjects are presented.

The primary endpoint has been met, showing a highly statistically significant advantage for daclizumab 150mg over IFN β-1a. the absolute rate reduction was 0.177 and a 45% reduction in the relapse rate was seen (as evidence by the relapse ratio of 0.55) and the upper bound of the 95% confidence interval was well below 1.00.

The clinical study report notes that there was a 38% reduction in the rate of severe or serious relapses in the daclizumab group compared with the IFN β-1a group (p=0.0021).

Sensitivity analyses

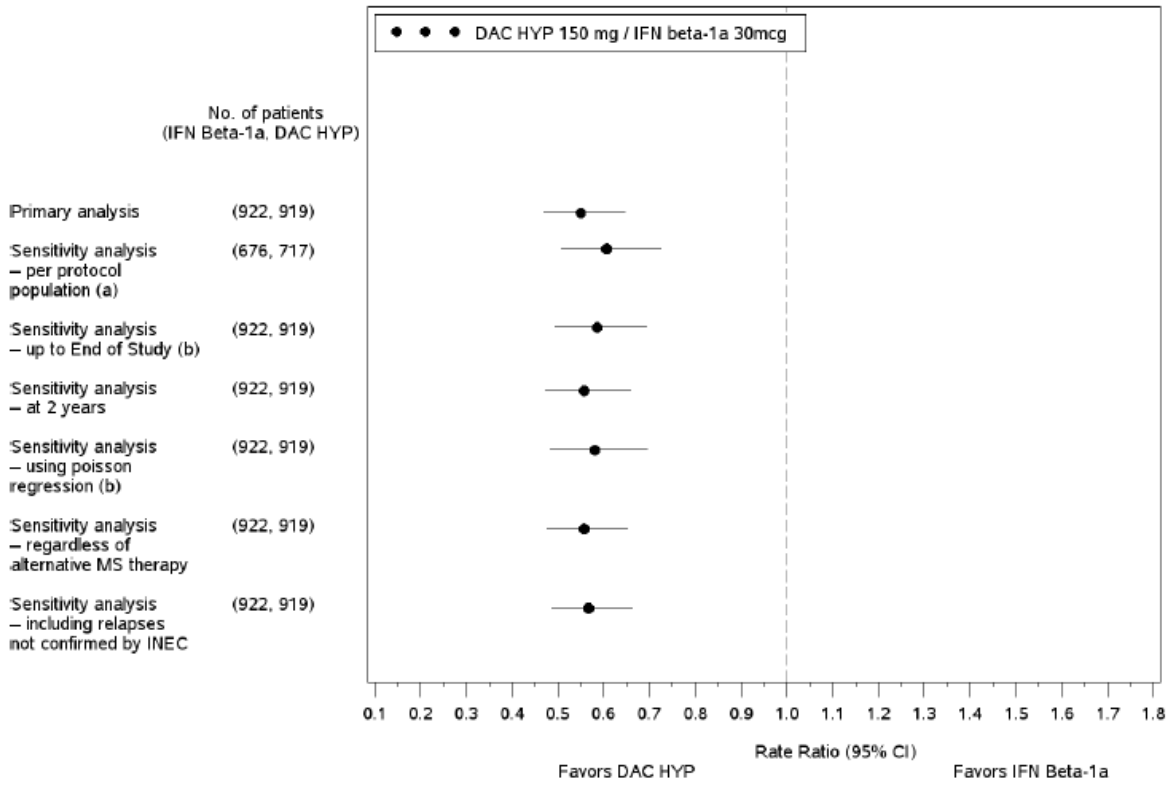
Multiple sensitivity analyses were performed to assess the robustness of the primary analysis. Alterations were made to the regression model parameters used to assess treatment effects on the annualized relapse rate:

- Using the per-protocol population instead of the ITT population

- using a Poisson regression model instead of a negative binomial regression model including all data until the end of study instead of the End of Treatment Period Visit
- censoring all subjects at the earliest of (1) the start of alternative MS medications, (2) end of treatment period visit date, or (3) 96 weeks after the first dosing date
- using a Poisson regression model instead of a negative binomial regression model. Adjusting the analysis only for the number of relapses in the 1 year prior to study entry
- including all INEC-confirmed relapses and follow-up time that occurred after the start of alternative MS medication
- including all protocol-defined relapses as assessed by the Investigator (whether or not INEC confirmed)

The results of these sensitivity analyses were all supportive and similar to the primary analysis presented above, indicating that the primary result was robust to a range of factors, including modelling assumptions and use of concomitant therapies that can affect annualized relapse rate.

Table 22 Annualised relapse rate – Summary of primary and sensitivity analysis results



(a) Estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (<=2.5 vs >2.5) and baseline age (<=35 vs >35).
(b) Estimated from a poisson regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (<=2.5 vs >2.5) and baseline age (<=35 vs >35). The model was adjusted for over-dispersion.

Subgroup analyses

Pre-specified subgroup analysis was performed for the primary and secondary efficacy endpoints. The subgroups were defined by the following demographic and baseline MS characteristics.

- gender
- age at baseline (≤ 35 years versus >35 years)

- geographic region
- weight (below median versus above median)
- number of relapses in the past 12 months (≤ 1 versus ≥ 2)
- number of relapses in the past 3 years (≤ 2 versus ≥ 3)
- baseline EDSS (EDSS ≤ 2.5 versus EDSS >2.5)
- baseline presence of Gd+ lesions (lesions present versus lesions absent)
- prior IFN-β use (yes versus no)
- prior immunomodulatory MS treatment excluding steroids (yes versus no)
- disease activity (high [≥ 2 relapses in the year prior to randomization and ≥ 1 Gd lesion at baseline MRI] versus low)

The definition of region was based not only on geography but also on the type of health care system and access to health care in each country and was defined as follows:

- Region 1: United States and Canada
- Region 2: Western European countries (Denmark, Finland, France, Germany, Greece, Ireland, Italy, Spain, Sweden, Switzerland, and United Kingdom), Australia, and Israel
- Region 3: Eastern European countries (Czech Republic, Georgia, Hungary, Moldova, Poland, Romania, Russia, Serbia, and Ukraine), Argentina, Brazil, India, and Mexico

The trend was in favour of daclizumab in all sub-groups with positive effect seen in various age groups or disease activity. As opposed to Study 205MS201 there was little difference according to prior MS treatment. Effect was also similar in patients with high or low disease activity (> 2 relapses in the last year and ≥ 1 Gd-enhancing lesion), with a point estimate actually lower in patients with high disease activity at baseline, and in patients with high or lower T2 lesion volume or with longer disease duration at baseline.

- **Secondary efficacy endpoints**

New or Newly Enlarging T2 Hyperintense Lesions at week 96

The adjusted mean number of new or newly enlarging T2 hyperintense lesions at Week 96 was 9.44 (95% CI: 8.46, 10.54) in the IFN β-1a treatment group and 4.31 (95% CI: 3.85, 4.81) in the daclizumab treatment group. Relative to IFN β-1a, daclizumab reduced the number of new or newly enlarging T2 lesions by 54.4% (95% CI: 46.9%, 60.8%; p<0.0001) at Week 96. The reductions in the number of new or newly enlarging T2 lesions at Week 96 were robust and consistent across all pre-specified subgroups.

Table 23 Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 96

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922	919
Number of subjects included in analysis (a)	841	864
Adjusted mean number of lesions at Week 96 (95% CI) (b)	9.44 (8.46, 10.54)	4.31 (3.85, 4.81)
Lesion mean ratio (compared to IFN beta-1a) (95% CI) (b)		0.46 (0.39, 0.53)
Percent reduction (compared to IFN beta-1a) (95% CI) (b)		54.4 (46.9, 60.8)
p-value vs IFN beta-1a (b)		<0.0001

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data are not imputed. Only observed new or newly enlarging T2 lesions at the last visit of the subject up to Week 96 visit is used in this analysis. 245 subjects with last new or newly enlarging T2 MRI observations taken prior to Week 96 assessment, and 1460 subjects with last new or newly enlarging T2 MRI observations taken at Week 96 assessment are included in the analysis.
(a) Subjects with baseline and at least one post-baseline MRI measurement are included in this analysis.
(b) Estimated from a negative binomial regression model, adjusted for baseline volume of T2 hyperintense lesions, history of prior IFN beta use and baseline age (<=35 vs >35). To account for the timing of the MRI measurement, the logarithmic transformation of the scan number of the MRI assessment will be included in the model as the 'offset' parameter.

Progression of Disability as Measured by EDSS Score

Confirmed disability progression was defined as a ≥ 1.0-point increase on the EDSS from a baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase on the EDSS from a baseline EDSS of 0 that was sustained for 12 weeks. The difference between treatment groups in confirmed disability progression was assessed using a Cox proportional hazards model, adjusted for baseline EDSS (EDSS ≤ 2.5 vs. EDSS >2.5), history of prior IFN β use, and baseline age (age ≤ 35 versus age >35 years).

In the primary analysis, the hazard ratio for daclizumab/IFN β-1a was 0.84 (95% CI: 0.66, 1.07), indicating daclizumab reduced the risk of disability progression by 16% (p=0.1575) compared with IFN β-1a.

Table 24 Summary of Time to 3-Month Sustained Disability Progression Measured by Increase in EDSS

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects progressed	140 (15)	121 (13)
Time (weeks) to progression (a)		
10th percentile	60.1	72.6
25th percentile	NA	NA
50th percentile	NA	NA
Estimated proportion progressed (a)		
24 weeks	0.036	0.035
48 weeks	0.081	0.064
72 weeks	0.114	0.095
96 weeks	0.143	0.120
120 weeks	0.161	0.148
144 weeks	0.203	0.162
Hazard ratio (DAC HYP/ IFN beta-1a) and 95% CI (b)		0.84 (0.66, 1.07)
p-value vs IFN beta-1a (b)		0.1575

NOTE 1: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.
2: Subjects are censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression.
3: Subjects with a tentative progression at the End of Treatment Period Visit (or the last EDSS assessment prior to alternative MS start date) and no confirmation assessment are censored at their last EDSS assessment.
4: For baseline EDSS assessment, the value obtained at Screening was used for 5 subjects (2 for the IFN beta-1a group and 3 for DAC HYP 150 mg group) and Week 12 for subject 3010125 in IFN beta-1a group.
(a) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.
(b) Based on Cox Proportional Hazards model, adjusted by baseline EDSS values as continuous variable, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

In the primary analysis of 12-week confirmed disability progression, all subjects who had a tentative disability progression and did not have an available confirmatory assessment were assumed to be nonprogressors and were censored at the time of the last assessment. A prespecified sensitivity analysis of 12-week confirmed disability progression was performed based on the alternative assumption that confirmed disability progression would occur at a similar rate as that for subjects who completed the confirmatory assessment in the trial (after adjustment for treatment group, baseline EDSS, change in EDSS at time of tentative progression, and presence of a relapse within the 29 days prior to the tentative progression. In this analysis, daclizumab reduced the risk of 12-week confirmed disability progression by 21% as compared with the IFN β-1a group (hazard ratio [daclizumab/IFN β-1a] of 0.79 [95% CI: 0.62, 1.00; p=0.0469]). An additional prespecified sensitivity analysis was carried out in which all tentative progressions with no confirmation assessment were assumed to be confirmed. In this analysis,

daclizumab also significantly reduced the risk of 12-week confirmed progression by 24% compared with the IFN β-1a group (hazard ratio [daclizumab/IFN β-1a] of 0.76 [95% CI: 0.61, 0.95; p=0.0157]).

Proportion of Subjects Free From Relapse

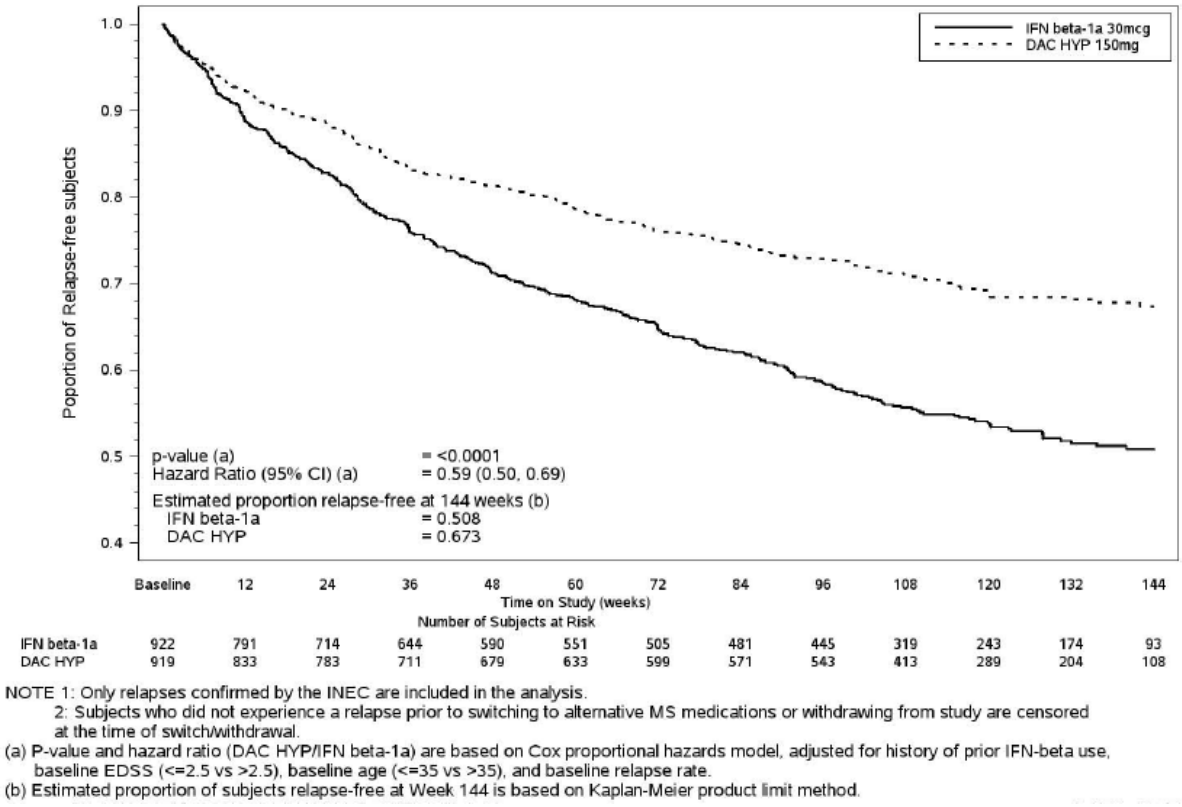
The primary analysis of this endpoint was based on INEC-confirmed relapses and included data from all subjects in the ITT population between the first dosing date and the subject's End of Treatment Period Visit or time of receiving alternative medication. No data were imputed.

Across the treatment period, 392 subjects (43%) in the IFN β-1a group and 260 subjects (28%) in the daclizumab group had an INEC-confirmed relapse. The Kaplan-Meier estimate for relapse-free subjects in the IFN β-1a and daclizumab groups was 71.2% and 81.2%, respectively, at 48 weeks; 58.5% and 72.9% at 96 weeks; and 50.8% and 67.3% at 144 weeks. The hazard ratio (daclizumab/IFN β-1a) for the risk of relapse was 0.59 (95% CI: 0.50, 0.69; p<0.0001), indicating that the risk of relapse was reduced by 41% in the daclizumab group compared to IFN β-1a.

Table 25 Proportion of Subjects Relapse Free

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects		
Relapsed	392 (43)	260 (28)
Relapse-free (a)	530 (57)	659 (72)
Estimated proportion of subjects relapse-free at (b)		
0 weeks	1.000	1.000
24 weeks	0.828	0.883
48 weeks	0.712	0.812
72 weeks	0.646	0.760
96 weeks	0.585	0.729
120 weeks	0.539	0.687
144 weeks	0.508	0.673
Time (weeks) to first relapse (b)		
10th percentile	11.1	18.1
25th percentile	39.0	80.4
50th percentile	145.4	NA
Hazard ratio for risk of relapse (DAC HYP/IFN beta-1a)		0.59
(95% CI) (c)		(0.50, 0.69)
p-value vs IFN beta-1a (c)		<0.0001

NOTE 1: Only relapses confirmed by INEC are included in this analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.
(a) Subjects who did not have a relapse.
(b) Based on the Kaplan-Meier product limit method.
(c) Based on Cox proportional hazards model, adjusted for baseline relapse rate, history of prior IFN beta use, baseline EDSS (EDSS <= 2.5 vs EDSS > 2.5) and baseline age (<=35 vs >35).



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawing from study are censored at the time of switch/withdrawal.
(a) P-value and hazard ratio (DAC HYP/IFN beta-1a) are based on Cox proportional hazards model, adjusted for history of prior IFN-beta use, baseline EDSS (<=2.5 vs >2.5), baseline age (<=35 vs >35), and baseline relapse rate.
(b) Estimated proportion of subjects relapse-free at Week 144 is based on Kaplan-Meier product limit method.

Figure 8 Time to first relapse (INEC confirmed relapses) – Study 205MS301

Change in MSIS-29 Physical Score at Week 52

The MSIS-29 includes 2 scales that examine the impact of MS from a subject's perspective: the 20-item Physical Impact scale and the 9-item Psychological Impact scale. Increased scores on these scales represent worsening from baseline and decreased scores represent improvement; a change of ≥ 7.5 points is considered clinically meaningful. The treatment effect on the proportion of subjects with a ≥ 7.5-point worsening from baseline in the MSIS-29 Physical Impact score was analyzed using a logistic regression model and adjusting for the baseline Physical Impact score, baseline BDI, history of prior IFN β use, and baseline age (age ≤ 35 versus age >35 years). Week 96 data were imputed for 202 subjects in the IFN β-1a group and 169 subjects in the daclizumab group.

At 96 weeks, 213 subjects (23%) in the IFN β-1a group had a ≥ 7.5-point worsening from baseline compared with 171 subjects (19%) in the daclizumab treatment group. The odds ratio (daclizumab/IFN-β 1a) was 0.76 (95% CI: 0.60, 0.95; p=0.0176), indicating that the risk of a clinically meaningful worsening on the subject-reported physical impact of MS was reduced by 24% in the daclizumab group compared with the IFN β-1a group.

The proportion of subjects with a ≥ 7.5-point worsening on the MSIS-29 Physical Impact score was lower in the daclizumab group than in the IFN β-1a group at each visit up to and including Week 96. Throughout the study, 14% to 19% of subjects in the daclizumab group and 19% to 23% of subjects in the IFN β-1a group had a ≥ 7.5-point worsening on MSIS-29 Physical Impact score.

Table 26 Proportion of Subjects With a ≥7.5-Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at Week 96

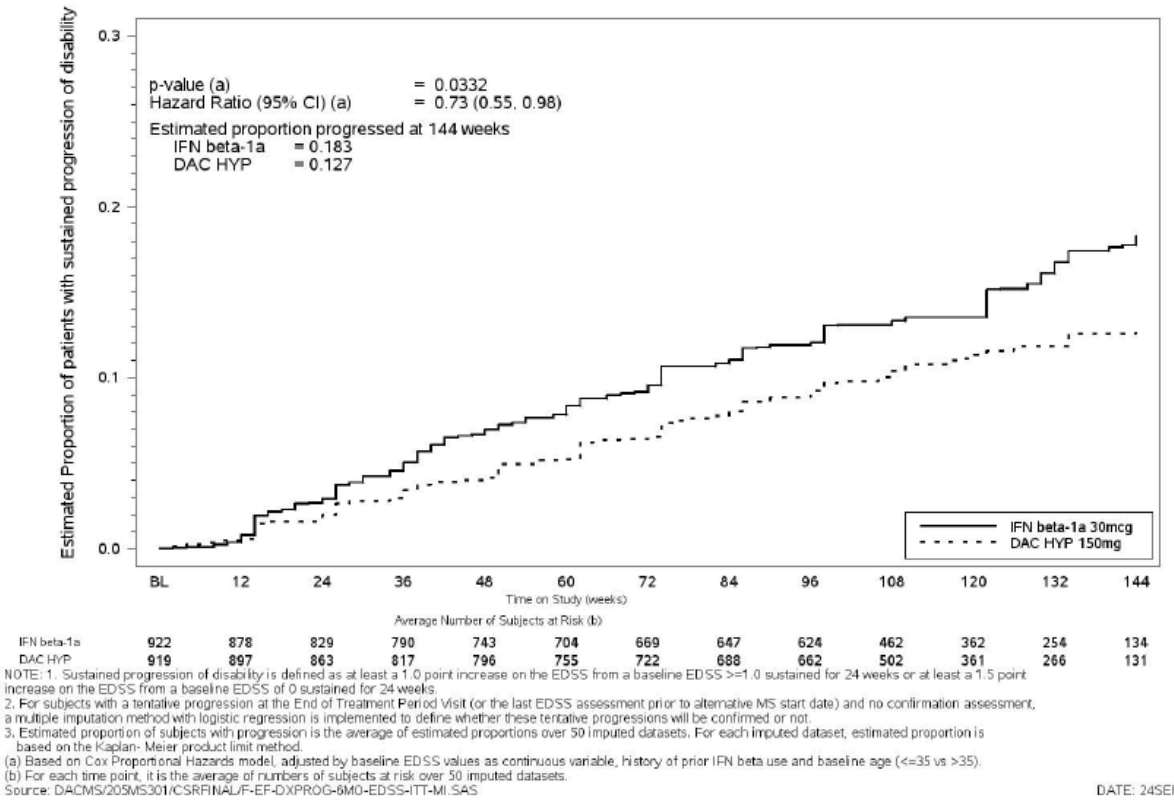
	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922	919
Number of subjects included in analysis (a)	912 (100)	906 (100)
Number of subjects with worsening MSIS-29 physical score at Week 96		
No	699 (77)	735 (81)
Yes	213 (23)	171 (19)
Odds ratio (DAC HYP/ IFN beta-1a) (95% CI) (b)		0.76 (0.60, 0.95)
p-value vs IFN beta-1a (b)		0.0176

NOTE 1: If a subject is missing data for less than 10 of the 20 items that make up the physical score, then the mean of the non-missing items will be used for the missing items. The number of subjects with imputed data was 3 for the IFN beta-1a group.
2: If the subject was missing 10 or more of the 20 items that make up the physical score, or missing the questionnaire entirely, or if the questionnaire was completed after the subject switched to alternative MS medication, a random effects model was used to estimate the MSIS-29 physical score. The number of subjects with imputed data was 202, 169 for the IFN beta-1a and DAC HYP 150 mg groups, respectively.
3: Numbers in parentheses are percentages.
(a) Subjects with available baseline assessments will be included in this analysis.
(b) Based on logistic regression model, adjusted for baseline MSIS-29 physical score, baseline BDI score, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

- **Tertiary endpoints**

- **24-week sustained disability progression**

Results of the protocol-specified analysis of 24-week confirmed disability progression show that daclizumab reduced the risk of 24-week confirmed disability progression by 27% compared with IFN β-1a (hazard ratio of 0.73 [95% CI: 0.55, 0.98]; p=0.0332).



NOTE: 1. Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 24 weeks.
2. For subjects with a tentative progression at the End of Treatment Period Visit (or the last EDSS assessment prior to alternative MS start date) and no confirmation assessment, a multiple imputation method with logistic regression is implemented to define whether these tentative progressions will be confirmed or not.
3. Estimated proportion of subjects with progression is the average of estimated proportions over 50 imputed datasets. For each imputed dataset, estimated proportion is based on the Kaplan- Meier product limit method.
(a) Based on Cox Proportional Hazards model, adjusted by baseline EDSS values as continuous variable, history of prior IFN beta use and baseline age (<=35 vs >35).
(b) For each time point, it is the average of numbers of subjects at risk over 50 imputed datasets.
Source: DACMS/205MS301/CSRFINAL/F-EF-DXPROG-6M0-EDSS-ITT-MI.SAS
DATE: 24SEP2014

Figure 9 Time to 6-Month Sustained Progression of Disability Measured by Increase in EDSS Using Multiple Imputation

The protocol-specified analysis of 24-week confirmed progression was performed using the same methodology that was used as a sensitivity analysis for 12-week confirmed progression. Overall, the same pattern of results was observed in the analysis of 24-week confirmed progression as for 12-week confirmed progression: when it was assumed that disability progression occurred in censored subjects at a similar rate as subjects who completed the confirmatory visit (after adjustment for baseline EDSS, change in EDSS at the time of tentative progression, treatment group, and the occurrence of recent MS relapse), the effect estimate favoring daclizumab over IFN β-1a was statistically significant. Furthermore, in an analysis in which all tentative progressions with no confirmation assessment are assumed to be confirmed, daclizumab reduced the risk of 24-week confirmed disability progression by 30% compared to IFN β-1a (hazard ratio of 0.70 [95% CI: 0.56, 0.89]; p=0.0034). When it was assumed that disability progression did not occur in any subject who was censored after a tentative progression, the risk of 24-week confirmed disability progression was reduced by 21% with daclizumab compared to IFN β-1a (hazard ratio of 0.79 [95% CI: 0.59, 1.06]; p=0.1186).

- **Change in EDSS score and change from baseline**

At Week 96, the median (minimum, maximum) scores were 2.00 (0.0, 7.0) and 2.00 (0.0, 6.5) respectively, in the IFN β-1a and daclizumab groups, representing median (minimum, maximum) changes of 0.0 (-3.0, 3.5) and 0.0 (-2.5, 4.0), respectively. The median (minimum, maximum) change at Week 144 was 0.00 (-3.0, 4.0) in the IFN β-1a group and 0.0 (-3.5, 3.5) in the daclizumab group.

- **Sustained Improvement in Disability as Measured by EDSS Score in Subjects With Baseline EDSS Score of ≥2**

Sustained improvement in disability was defined as at least a 1.0-point decrease on the EDSS from baseline EDSS assessment ≥2.0 that was sustained for 12 weeks. Among the subjects with a baseline EDSS score of ≥2, a similar proportion of subjects in both treatment groups experienced an improvement in disability: 105 subjects (17%) in the IFN β-1a group and 108 subjects (17%) in the daclizumab group

- **Change in Multiple Sclerosis Functional Composite (MSFC) score over 48 and 96 weeks**

At Week 96, the median increases (indicating improvement) from baseline in the MSFC composite z-score were 0.055 and 0.091 in the IFN β-1a and daclizumab groups, respectively (p=0.0007), indicating greater improvement in the daclizumab group relative to IFN β-1a. The increases at each 12-week timepoint up to Week 96 were all greater in the daclizumab group compared with the IFN β-1a group. At Week 48, the median increase from baseline in the MSFC composite z-score was 0.058 in the IFN β-1 group and 0.071 in the daclizumab group (p=0.0461).

Results for the MSFC component z-scores (T25FW, 9HPT, PASAT 3) also indicated greater improvement in ambulation, dexterity, and cognition in the daclizumab group compared to the IFN β-1a group. The median changes at Week 96 were as follows:

- T25FW: Median change (25th, 75th percentile) of -0.017 (-0.124, 0.075) in the IFN β-1a group and 0.00 (-0.099, 0.083) in the daclizumab group (p=0.0060)
- 9HPT: Median change (25th, 75th percentile) of 0.017 (-0.273, 0.291) in the IFN β-1a group and 0.063 (-0.195, 0.356) in the daclizumab group (p=0.0016)

PASAT 3: Median change (25th, 75th percentile) of 0.177 (-0.088, 0.442) in the IFN β-1a group and 0.177 (-0.088, 0.530) in the daclizumab group (p=0.0411)

- **Visual Function Test (VFT)**

VFT scores are expressed as the number of letters correctly identified on the low-contrast Sloan letter chart at 100%, 2.5%, and 1.25% contrast. In the prespecified analysis, the mean change at Week 96 for 1.25% contrast was evaluated using an analysis of covariance (ANCOVA) model after imputing missing data using LOCF. In this analysis, the mean change from baseline at Week 96 was -1.51 in the IFN β-1a group and -1.34 in the daclizumab group (p=0.5712).

- **Change in oral Symbol Digit Modalities Test (SDMT)**

The prespecified approach was an ANCOVA model on the change from baseline after imputing missing data using an LOCF approach. In this analysis, the mean change from baseline at Week 96 was 2.96 in the IFN β-1a group and 3.42 in the daclizumab group (p=0.1552).

- **Proportion of subjects who are free of disease activity**

Subjects were considered free of disease activity if they were without clinical or radiological activity. Clinical activity included an assessment of relapses and of disease progression, and radiological activity included an assessment of Gd+ lesions and new or enlarging T2 lesions. A greater proportion of subjects in the daclizumab group (198 subjects [22%]) remained free of disease activity as compared with the IFN β-1a group (116 subjects [13%]). The odds ratio (daclizumab/IFN β-1a) was 2.009 (95% CI: 1.554, 2.598; p<0.0001).

- **Change in quality of life on the European Quality of Life, 5 dimensions (EQ-5D and EQ-VAS), MSIS-29 Psychological Impact score, and MSIS-29 Physical Impact score**

-EQ-5D VAS: Numerically greater improvement relative to IFN β-1a was observed in the daclizumab group at Week 48. Scores increased over time in the daclizumab group and remained relatively unchanged in the IFN β-1a group. At Week 72, mean changes were 1.25 and 2.60 in the IFN β-1a and daclizumab groups, respectively (p=0.02200; by Week 96, mean changes were 0.33 and 2.69 (p= 0.0006).

-The results of the EQ-5D index score reflected improved health status in the daclizumab group as compared with the IFN β-1a group, with greater improvement at Weeks 48 and 96 (Table 147). By Week 96, the mean increases in the EQ-5D index scores were 0.004 and 0.028 in the IFN β-1a and daclizumab groups, respectively (p=0.0048).

-The differences in the MSIS-29 Physical Impact scores between the daclizumab and IFN β-1a groups were evident as early as 24 weeks (p=0.0322) and persisted up to Week 96. The mean ± SD change in the MSIS-29 Physical Impact score from Baseline to Week 96 was a worsening of 1.15 ± 14.064 points in the IFN β-1a group and an improvement of 0.84 ± 14.156 points in the daclizumab group (p = 0.0008).

- **Whole brain volume**

The annualized Percent Brain Volume Change (PBVC) was reduced in the daclizumab group compared with the IFN β-1a group during the 2 prespecified time periods of baseline to Week 24 (median annualized PBVC of -0.745 for IFN β-1a versus -0.674 for daclizumab; p=0. 0325) and Week 24 to Week 96, (median annualized PBVC -0.549 for IFN β-1a vs. -0.511 for daclizumab; p<0.0001).

- **Total number and volume of new T1 hypointense lesions, T2 hyperintense lesions, and Gd+ lesions on brain MRI scans**

Reductions in the tertiary MRI endpoints of brain atrophy and T2, T1, and Gd+ lesion count and volume were also consistent with the effect on new or enlarging T2 lesions. The treatment effect of daclizumab on new or enlarging T2 lesions and other MRI endpoints was detectable by Week 24 (p<0.0001) and was

sustained through to the Week 96 MRI at a similar magnitude. Daclizumab produced treatment-related reductions in brain atrophy (p<0.0001).

- **MRI variables over 24, 48 and 96 weeks**

Statistical significant difference was noted for the number of new non enhancing T1 Hypointense lesions at Weeks 24, 96, and 144 (p<0.0001), and at week 24 for the number of Gd-Enhancing lesions or Number of New or Newly Enlarging T2 Hyperintense Lesions; similar results were seen for the volume of these lesions. Of note the median decrease in T2 hyperintense lesion volume with IFN β-1a and daclizumabwas 0.27% and 1.44%, respectively (p=0.0188) at week 24 and the median T2 lesion volume increase from baseline to week 96 was 3.76% and 0.20%, respectively (p<0.0001).

- **Ancillary analyses**

Subgroup analyses demonstrated that the effect of daclizumab on the primary endpoint was evidenced across all prespecified demographic and baseline characteristic subgroups. There was minor variation in treatment effect estimates across the multiple subgroups; however, the point estimates for all endpoints and subgroups favoured daclizumab, and there was no convincing evidence for effect modification by any of the prespecified characteristics that were analyzed. An ad hoc analysis of ARR by body weight quartiles demonstrated a consistent treatment effect favoring daclizumab over IFN β-1a across all quartiles.

2.5.1.2.3. Effect on disability progression in all forms of RMS

In order to gain the full RMS indication the applicant was asked to demonstrate a positive effect on disability progression in all forms of RMS, including the relapsing forms of Secondary Progressive Multiple Sclerosis. In the clinical development of daclizumab in MS, the 2 pivotal trials were of sufficient duration and size that certain subjects included in these trials could during the trials be identified as having SPMS with superimposed relapses based on the observation of sustained disability progression that occurred independently of, or in the absence of, clinical relapses. Furthermore, analysis of these subjects provided evidence that daclizumab was more effective than IFN β-1a at preventing the progression of sustained disability progression that occurred independently of clinical relapses. This finding, in conjunction with the analyses provided in the response to the CHMP query, demonstrating efficacy of daclizumab in subjects with both highly active (approximately 40% of subjects) and less active (approximately 60% of subjects) forms of MS, demonstrated that daclizumab has efficacy across a broad spectrum of MS subjects and was considered sufficient to support an indication for “relapsing forms of MS.”

As shown in the following tables (see Table 27 and Table 28), data and analyses were provided showing evidence for the efficacy of daclizumab compared to IFN β-1a for the prevention of confirmed neurologic worsening independent of relapse activity and in the relapse-free population in the trial. The efficacy results demonstrated consistent and meaningful trends favoring daclizumab over IFN β-1a across the range of baseline EDSS categories including ≥3.5, ≥4.0, and ≥4.5, indicating that the benefit was not confined to subjects with lower baseline EDSS scores. The hazard ratios (daclizumab/IFN β-1a) demonstrate that the risk of worsening in neurologic function based on the composite of all 3 endpoints was reduced by approximately 25% in the daclizumab arm relative to IFN β-1a in all baseline EDSS categories. Overall, the evidence of benefit was strongest on preventing the 6-month confirmed 20% decline on the T25FW gait measure, with an approximate 40% reduction in the risk of worsening in the daclizumab group compared to IFN β- 1a. This result is particularly relevant to the relapsing SPMS population, as decline in gait is typically the strongest contributor to EDSS decline in the early SPMS period.

Finally, the efficacy results were also consistent in the relapse-free population, providing additional confidence that the benefits on disease progression were not related to the effect of daclizumab on the prevention of clinical relapses. These data can support the indication of Daclizumab 150 mg for relapsing forms of MS with added information to be provided in section 5.1 of the SmPC regarding the effect in relapse-free patients with EDSS ≥3.5

Table 27 Summary of Confirmed Progression Independent of Relapse in Study 301

Proportion subjects with confirmed progression at 144 weeks independent of relapse

EDSS range	Outcome	IFN beta-1a 30 mcg	DAC HYP 150 mg	HR (95% CI) (b)
>=3.5	Number of subjects evaluated	291	260	
	Composite	0.331	0.236	0.73 (0.51, 1.04)
	Timed 25-Foot Walk	0.241	0.153	0.66 (0.43, 1.01)
	Nine-Hole Peg (a)	0.078	0.070	0.92 (0.46, 1.83)
	EDSS	0.153	0.127	0.86 (0.52, 1.43)
>=4.0	Number of subjects evaluated	179	159	
	Composite	0.391	0.285	0.73 (0.48, 1.11)
	Timed 25-Foot Walk	0.275	0.182	0.66 (0.40, 1.10)
	Nine-Hole Peg (a)	0.101	0.085	0.79 (0.36, 1.75)
	EDSS	0.193	0.157	0.84 (0.47, 1.49)
>=4.5	Number of subjects evaluated	97	84	
	Composite	0.445	0.344	0.77 (0.44, 1.33)
	Timed 25-Foot Walk	0.297	0.173	0.58 (0.29, 1.15)
	Nine-Hole Peg (a)	0.094	0.085	0.85 (0.28, 2.54)
	EDSS	0.281	0.237	0.91 (0.47, 1.76)

Note: Estimated proportion of subjects with confirmation is based on the Kaplan Meier product limit method.
(a) Analysis excludes subjects with missing baseline data for Nine-Hole Peg Test.
(b) Based on Cox Proportional Hazards model, adjusted by baseline value of the corresponding MSFC component or EDSS, history of prior IFN beta use, and baseline age (age <= 35 vs age >35). Analysis on composite adjusted for baseline EDSS, baseline Timed 25-Foot Walk Test, baseline Nine-Hole Peg Test, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

Table 28 Summary of Confirmed Progression in Relapse-free Population in Study 301

Proportion subjects with confirmed progression at 144 weeks and relapse free

EDSS range	Outcome	IFN beta-1a 30 mcg	DAC HYP 150 mg	HR (95% CI) (b)
>=3.5	Number of subjects evaluated	163	154	
	Composite	0.234	0.143	0.67 (0.36, 1.22)
	Timed 25-Foot Walk	0.164	0.091	0.49 (0.23, 1.03)
	Nine-Hole Peg (a)	0.064	0.031	0.50 (0.15, 1.67)
	EDSS	0.087	0.072	1.16 (0.46, 2.93)
>=4.0	Number of subjects evaluated	101	88	
	Composite	0.284	0.134	0.50 (0.22, 1.15)
	Timed 25-Foot Walk	0.189	0.074	0.34 (0.12, 0.97)
	Nine-Hole Peg (a)	0.066	0.000	NA
	EDSS	0.153	0.092	0.76 (0.27, 2.18)
>=4.5	Number of subjects evaluated	56	45	
	Composite	0.392	0.172	0.49 (0.17, 1.39)
	Timed 25-Foot Walk	0.221	0.056	0.23 (0.05, 1.13)
	Nine-Hole Peg (a)	0.095	0.000	NA
	EDSS	0.290	0.145	0.62 (0.20, 1.98)

Note: Estimated proportion of subjects with confirmation is based on the Kaplan Meier product limit method.
(a) Analysis excludes subjects with missing baseline data for Nine-Hole Peg Test.
(b) Based on Cox Proportional Hazards model, adjusted by baseline value of the corresponding MSFC component or EDSS, history of prior IFN beta use, and baseline age (age <= 35 vs age >35). Analysis on composite adjusted for baseline EDSS, baseline Timed 25-Foot Walk Test, baseline Nine-Hole Peg Test, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

2.5.1.2.4. Clinical studies in special populations

MS is a disease predominantly affecting young adult females, and therefore, age and gender were preselected as principal patient demographics for evaluation. Because MS is encountered mostly among individuals of Caucasian, Northern European descent, only a small proportion of non-white subjects enrolled in Studies 201 and 301, and subgroup analyses by race were not conducted. Lastly, several baseline disease characteristics have been identified that are predictive of a potentially more aggressive versus less aggressive clinical course, including evidence of established neurological disability on the EDSS, early versus longer duration of RRMS disease, relapse activity over the 12 months prior to entering study, exposure to previous DMT versus treatment naïve, presence versus absence of T1 Gd+ lesions, and total disease burden on T2 lesion volume. Therefore, subgroups defined by these baseline disease characteristics were also included in the analyses in both clinical studies.

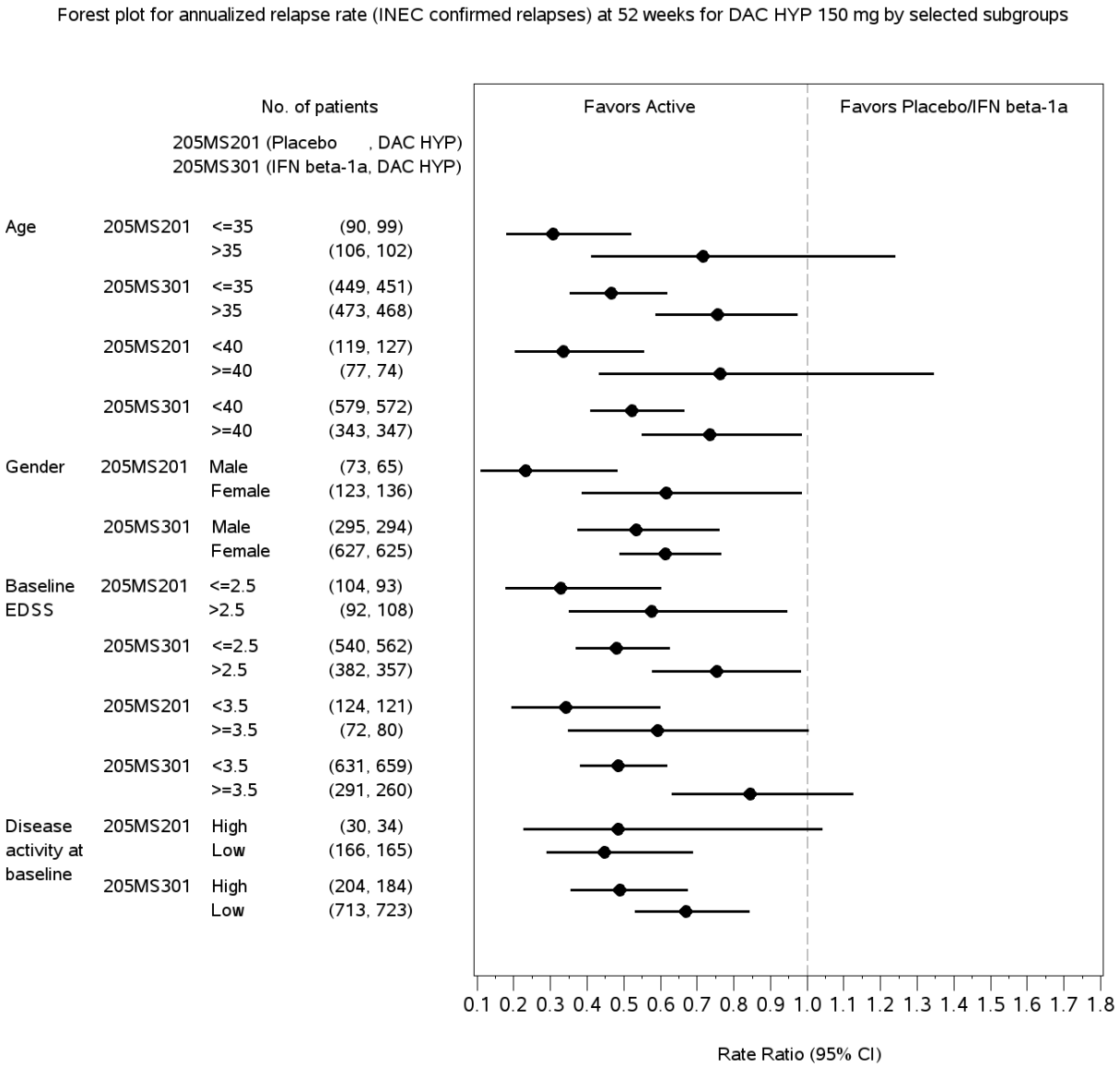
The endpoints for the subgroup analyses consisted of the primary clinical efficacy parameter of annualized relapse rate and the supportive neuroimaging parameters of change from baseline in new or newly enlarging T2 lesions and new Gd lesions. The endpoints of the proportion of subjects with relapse, confirmed disability progression (Study 301 only), and the proportion of subjects with worsening on the MSIS-29 (Study 301 only) were also evaluated.

In both pivotal studies, a greater treatment effect was observed for Daclizumab 150 mg relative to control across all prespecified demographic and baseline characteristic subgroups for each of the efficacy endpoints analyzed (Figure below). A pooled analysis of annualized relapse rate over 1 year was conducted in which data for subjects in the Daclizumab 150 mg dose groups of Studies 201 and 301 were pooled and compared to the results for the placebo group in Study 201 and the IFN β-1a group of Study 301.

The results of the pooled analysis favored daclizumab treatment over control for all subgroups and show that the annualized relapse rate for daclizumab-treated subjects was consistent across the prespecified demographic and disease characteristics subgroups. The results demonstrate that the daclizumab efficacy observed in the ITT analyses for Studies 201 and 301 was not driven disproportionately by particular RRMS patient subgroups. In addition, daclizumab effectively reduced disease activity in every subgroup across the spectrum of RRMS patients. Based on the cross-study population PK analysis, body weight accounted for less than 40% of the inter-subject variability in daclizumab clearance. The impact of body weight on daclizumab exposure does not appear to be clinically relevant as the ARRs in Study 301 were similar across subgroups based on body weight quartiles.

Consistent with the impact seen on clinical MS relapses across the prespecified subgroups in Studies 201 and 301, daclizumab treatment also demonstrated a robust and substantial effect compared to placebo or active comparator treatment on reducing focal areas of inflammation and tissue destruction defined by the MRI endpoints of the number of new or newly enlarging T2 lesions and the number of new Gd+ lesions.

Figure 10 Forest Plot for Annualized Relapse Rate (INEC-Confirmed Relapses) at 52 Weeks for Daclizumab 150 mg by Selected Subgroups



NOTE: Rate ratios and 95% CI are estimated from a negative binomial (NB) or Poisson (if NB failed to estimate) regression adjusted for baseline EDSS (<=2.5 vs. >2.5), baseline age (<=35 vs. >35) and number of relapses in the 1 year prior to study entry for 205MS201, and adjusted for the baseline relapse rate (number of relapses in the 3-years prior to study entry divided by 3), history of prior IFN beta-1a use (yes/no), baseline EDSS (EDSS <= 2.5 versus EDSS > 2.5) and baseline age (age <= 35 versus age >35) for 205MS301.

SOURCE: DACMS/BLA/BLA/F-ISE-ARR-FOREST-TRT.SAS DATE: 30SEP2014

Efficacy by Antibody Status

The impact of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) on efficacy has been explored by summarizing key efficacy endpoints by AB status.

Treatment-emergent ADAs to Daclizumab150 mg were observed in 4% and 19% of evaluable subjects in Studies 201 and 301, respectively. The majority (12% [110/913]) of the treatment emergent ADA responses in Study 301 were transient (defined as positive evaluations other than final evaluations that are non-consecutive or are consecutive but <74 days apart), and the minority (7% [65/913]) were persistent. Treatment-emergent NAbs to Daclizumab150 mg were observed in 3% and 8% of evaluable

subjects in Studies 201 and 301, respectively. The majority of ADA and NAb reactivity to daclizumaboccurred early during treatment and decreased with continuing daclizumab treatment.

The impact of ADAs and NAbs on efficacy was explored by summarizing clinical endpoints (relapses) and radiological endpoints. In Study 301, the adjusted annualized relapse rate was comparable for both AB-positive and AB-negative daclizumab-treated subjects. Similarly, there was no detectable impact of ADAs or NAbs on the number of Gd+ lesions or the number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 96. With the limitations of the low incidence of AB-positive subjects in Study 201, the adjusted annualized relapse rate was similar between daclizumab-treated ADA-positive and ADA-negative subjects. The percentage of subjects that were relapse-free at 1 year was comparable for ADA-positive and ADA-negative groups. Similar results were observed for the Nab positive or Nab-negative subjects.

The mean number of new Gd lesions at 1 year in Study 201 was similar for ADA-positive and ADA-negative daclizumab-treated subjects, and the percentage of subjects with no Gd+ lesions at 1 year on cranial MRI was similar in the ADA-positive and ADA-negative groups. Similar results were observed for the NAb-positive or NAb-negative subjects.

Overall, immunogenicity to daclizumab was typically transient and most often occurred during the first year of treatment. There was no discernible impact of ADAs or NAbs on efficacy during treatment with daclizumab.

Redefined “high disease activity”

The applicant redefined “high disease activity” and this modified definition added a second criterion to the definition used in the applicant’s primary analysis as shown below.

- Subjects with 2 or more relapses in 1 year, and with 1 or more Gd-enhancing lesions on brain MRI, or
- Subjects who failed to respond to a full and adequate course (at least 1 year of treatment) of prior DMT treatment, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years

Subjects who did not meet the criteria for high disease activity were classified in our analyses as having low/unknown disease activity.

To facilitate the assessment of benefit/risk based on this new definition of high disease activity, analyses were performed on the data from Study 201 and Study 301 for the following endpoints by baseline disease activity level:

- Overall summary of adverse events (AEs)
- Incidence of maximum values in liver function tests (Study 301 only)
- Annualized relapse rate (using INEC confirmed relapses)
- Number of new or newly enlarging T2 lesions
- 6-month sustained disability progression

Study 201

In Study 201, the overall AE profile was similar for the subjects with high and low/unknown disease activity at baseline. The incidence of AEs and SAEs reported were also similar among subjects with high

disease activity and low/unknown disease activity. Notably the incidence of AEs in the high and low disease activity subgroups of the total daclizumab group was similar for events in the Infections and Infestations SOC (53% and 52%, respectively) and the Skin and Subcutaneous Tissue Disorders SOC (16% and 21%, respectively).

The results of the analyses of annualized relapse rate and new or newly enlarging T2 lesions by baseline disease activity demonstrate the superiority of daclizumab over placebo for both the high and low/unknown disease activity subgroups. The reductions in the annualized relapse rate in the Daclizumab 150 mg group relative to placebo were similar, with a 52% reduction (p=0.0493) in the high disease activity group and a 54% reduction (p=0.0003) in the low/unknown disease activity. In the analysis of new or newly enlarging T2 lesions, the reduction relative to placebo was greater in the high disease activity group (78%, p<0.0001) than in the low/unknown disease activity group (66%, p<0.0001).

In the analyses of disability progression, treatment with Daclizumab 150 mg was associated with a markedly lower rate of 6-month sustained progression compared to placebo in both the high disease activity group (hazard ratio=0.23, p=0.2034) and the low/unknown disease activity group (hazard ratio=0.24, p=0.0093).

Study 301

As was the case in Study 201, there were no notable imbalances in the safety data between the high and low/unknown disease activity groups in Study 301. The incidence of SAEs was greater in subjects with high disease activity as compared to subjects with low disease activity in both treatment groups, suggesting the differences were associated with baseline disease severity and were not indicative of treatment-related differences. In the daclizumab arm, the incidence of AEs was slightly higher in the high disease activity subgroup as compared to the low disease activity subgroup for the Infections and Infestations SOC (70% vs. 62%) and the Skin and Subcutaneous Disorders SOC (41% vs. 62%). However, a similar trend was also seen in the IFN β-1a group, which suggests the differences are primarily a function of greater disease severity in these subjects.

Maximum values for liver function tests were also similar in the high and low/unknown disease activity groups of Study 301. Most subjects in both subgroups had maximum values that were between $\leq 3 \times$ ULN. The incidence of maximum values $\geq 5 \times$ ULN was low and similar between the disease activity subgroups and the daclizumab and IFN β-1a arms.

The results of the analyses of annualized relapse rate and new or newly enlarging T2 lesions by baseline disease activity demonstrate the superiority of daclizumab over IFN β-1a for both the high and low/unknown disease activity subgroups, with highly significant p values (<0.0001). For annualized relapse rate, the effect relative to IFN β-1a was greater in the high disease activity group (rate ratio 0.497: 95% CI 0.397, 0.621) than in the low/unknown disease activity group (rate ratio=0.614: 95% CI 0.490, 0.770). For new or newly enlarging T2 lesions, the results by baseline activity were comparable (reductions of 53.7% and 52.3%, respectively, for high and low/unknown disease activity).

In Study 301, there was a 43% reduction in 6-month sustained disability progression with daclizumab compared to IFN β-1a in the high disease activity subgroup (HR=0.57, p=0.0102). No significant difference was evident between treatment groups in the low/unknown disease activity group (HR=0.89, p=0.5662). The stronger treatment effect in the high disease activity subgroup may be due to a higher rate of disease progression in the IFN β-1a group, which provides more power to detect a treatment benefit. Conversely, the low rate of disease progression in the IFN β-1a arm provides less power to detect a treatment effect in the low disease activity subgroup. A similar pattern has been seen in other MS development programs in which a significant treatment benefit over IFN β-1a has been difficult to establish when there is a low progression rate [Cohen 2012] [Coles 2012]. Nevertheless, the clearly

superior findings of efficacy against disability progression compared to placebo in the low disease activity subgroup of Study 201 provide evidence that daclizumab does have a beneficial effect on disability progression in these subjects.

The results of these analyses demonstrate that the benefit/risk profile of daclizumab seem favourable when high disease activity is redefined based on the amended definition. The overall safety profile of daclizumab is consistent in subjects with low and high disease activity at baseline in both studies. Likewise, daclizumab provides a meaningful and consistent efficacy benefit over placebo and IFN β-1a whether measured in terms of relapses (annualized relapse rate), number of new/newly enlarging T2 lesions, or disability progression in subjects with both high and low disease activity at baseline. The differences between subgroups for some of the safety and efficacy results in both studies were generally observed in both the daclizumab and control groups and were consistent with the greater level of disease activity at baseline.

2.5.1.2.5. Analysis performed across trials (pooled analyses AND meta-analysis)

In both pivotal studies, a greater treatment effect was observed for daclizumab 150 mg relative to control across all pre-specified demographic and baseline characteristic subgroups for each of the efficacy endpoints analysed. A pooled analysis of annualized relapse rate over 1 year was conducted in which data for subjects in the Daclizumab 150 mg dose groups of Studies 201 and 301 were pooled and compared to the results for the placebo group in Study 201 and the IFN β-1a group of Study 301.

The results of the pooled analysis favoured daclizumab treatment over control for all subgroups and show that the annualized relapse rate for daclizumab-treated subjects was consistent across the prespecified demographic and disease characteristics subgroups. The results demonstrate that the daclizumab efficacy observed in the ITT analyses for Studies 201 and 301 was not driven disproportionately by particular RRMS patient subgroups. In addition, daclizumab effectively reduced disease activity in every subgroup across the spectrum of RRMS patients. Based on the cross-study population PK analysis, body weight accounted for less than 40% of the inter-subject variability in daclizumab clearance. The impact of body weight on daclizumab exposure does not appear to be clinically relevant as the ARRs in Study 301 were similar across subgroups based on body weight quartiles.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal studies were designed and carried out with adequate methodology to assess the main objectives. The selected comparator was IFN β-1a and it is considered acceptable, although it is probably the least effective form of IFN β treatment in RRMS.

No significant deviation was observed from current guidelines regarding pivotal trials. The published guidance suggests a 5 year period to assess maintenance of effect on disease progression and although this has not been accomplished the development programme is still quite comprehensive.

Efficacy data and additional analyses

The efficacy of daclizumab has been tested in 2 randomized, double-blind, controlled, pivotal studies. In the first study (Study 201 see 2.5.1.2.1.), the efficacy of daclizumab was compared to placebo, and in the other study (Study 301 see 2.5.1.2.2.), the efficacy of daclizumab was compared to a current standard of MS treatment, IFN β-1a. Both of these studies demonstrated consistent and robust treatment effects of daclizumab across well-validated clinical, radiographic, and patient-reported MS outcome measures. The

effects of daclizumab were apparent after the first dose as defined radiographically and within 3 months as defined by clinical endpoints. The benefits of daclizumab were then sustained over 3 years during continuous treatment.

Both clinical studies were designed to enrol a broad population of RRMS patients who had experienced relapses. The mean age of subjects was approximately 36 years, and the percentage of subjects with highly active MS (defined as having ≥ 2 relapses in the prior year and ≥ 1 Gd+ lesion on baseline MRI) at study entry ranged from 16% to 21%. The two studies enrolled subjects across a broad geographic catchment area, representing a diversity of MS practice patterns and healthcare systems. In both studies, a minority of enrolled subjects had received prior DMT, but the proportion was higher in Study 301 (41%) compared to Study 201 (20%).

The primary endpoint of both Studies 201 and 301 was the annualized relapse rate. Both studies demonstrated a robust effect of daclizumab on the reduction in clinical MS relapses: a 54% reduction versus placebo in Study 201 and a 45% reduction versus IFN β-1a in Study 301. The effect was consistent for subject-reported relapses, protocol defined relapses, and INEC-confirmed relapses. The observed relapse rate in the daclizumab-treated subjects was highly consistent at common time points across the two studies and was sustained over the duration of therapy: 0.211 over 1 year in Study 201 versus 0.249 over 1 year in Study 301. The annualized relapse rate for severe or serious relapses in the daclizumab arm at 1 year was 0.096 in Study 201 and 0.094 in Study 301, representing a 67% reduction relative to placebo ($p < 0.0001$) in Study 201 and a 34% reduction relative to IFN β-1a ($p = 0.0117$) in Study 301. The results of the analyses of annualized relapse rate in Studies 201 and 301 were supported by analyses of the proportion of subjects who relapsed. The proportion of subjects on daclizumab who relapsed after 1 year of treatment was 19% in both Studies 201 and 301. This represented a 55% reduction in the risk of relapse compared to placebo in Study 201 and a 39% reduction at 1 year compared to IFN β-1a in Study 301.

Consistent with the impact seen on clinical MS relapses, daclizumab demonstrated a robust and substantial effect on reducing focal areas of inflammation and tissue destruction defined by MRI in comparison to placebo and IFN β-1a. daclizumab treatment resulted in a 70% reduction in new or newly enlarging T2 lesions compared to placebo at 1 year in Study 201 and a 54% reduction compared to IFN β-1a at 2 years in Study 301 ($p < 0.0001$ for both comparisons). The number of new or newly enlarging T2 lesions in the Daclizumab 150 mg treatment group was consistent at similar time points in Studies 201/202 when compared to Study 301 (adjusted mean of 1.55 and 2.16 lesions at Week 24 and 2.83 and 4.31 lesions at Week 96). Since Gd enhancement typically lasts for only about 3 weeks, analysis of Gd+ lesions provides an informative way to assess the maintenance of efficacy over time. On this endpoint, the effect of daclizumab was highly consistent across the 2 studies, with a mean of 0.5 Gd+ lesions at Week 24 in both Studies 201 and 301 and 0.3 Gd+ lesions at 2 years in the Studies 201/202 compared to 0.4 Gd+ lesions in Study 301. Analysis of other MRI endpoints across studies such as T2 lesion volume and the number and volume of T1 hypointense black holes across Studies 201/202 and 301 demonstrated a consistent and robust effect of daclizumab that was present by Week 24 and sustained for the duration of daclizumab treatment.

In both pivotal studies, there was evidence that daclizumab reduced the risk of confirmed disability progression. In Study 201, daclizumab reduced the risk of 12-week confirmed disability progression by 57% relative to placebo ($p = 0.0211$) and the risk of 24-week confirmed disability progression by 76% ($p = 0.0037$). In Study 301, daclizumab reduced the risk of 12-week confirmed disability progression by 16% ($p = 0.1575$; not statistically significant) and the risk of 24-week confirmed disability progression by 27% ($p = 0.0332$). The differences in the daclizumab efficacy estimates for disability progression between Studies 201 and 301 are consistent with the established effect of IFN β-1a on confirmed

disability progression compared to placebo (37% vs. placebo in registrational studies). Overall, the magnitude of the treatment effect on confirmed disability progression against IFN β-1a in Study 301 (16% to 27% reduction) is confirmatory of the 57% to 76% reduction in confirmed disability progression against placebo in Study 201, recognizing the effect of IFN β-1a on this endpoint. Furthermore, the observed rates of disability progression during daclizumab treatment were consistent across Studies 201 and 301. In Study 301, confirmed disability progression was common after a tentative disability progression among subjects with at least one tentative disability progression in the trial: 35% for 12-week confirmed progression and 24% for the 24-week confirmed progression. Censoring after a tentative disability progression was nearly twice as common in the IFN β-1a group compared to the daclizumab group (43 vs. 24 for the 12-week confirmed progression), reflecting a proportionally higher number of tentative disability progressions in the IFN β-1a arm of the trial. While the number of subjects censored after a tentative disability progression (n = 67) was small relative to the total number of subjects with a tentative disability progression in the trial (n = 736), assumptions made about disability progression in these censored subjects impacted whether the test of statistical significance for disability progression was above or below the 0.05 significance threshold in Study 301. Pre-specified analyses of disability progression in Study 301 supported a significant treatment effect of daclizumab over IFN β-1a on both 12- and 24-week confirmed disability progression analyses, except when analysed under the assumption that disability progression did not occur in any patient who was censored after a tentative disability progression.

In order to gain the full RMS indication the applicant was asked to demonstrate a positive effect on disability progression in all forms of RMS, including the relapsing forms of Secondary Progressive Multiple Sclerosis. In the clinical development of daclizumab in MS, the 2 pivotal trials were of sufficient duration and size that certain subjects included in these trials could during the trials be identified as having SPMS with superimposed relapses based on the observation of sustained disability progression that occurred independently of, or in the absence of, clinical relapses. Furthermore, analysis of these subjects provided evidence that daclizumab was more effective than IFN β-1a at preventing the progression of sustained disability progression that occurred independently of clinical relapses. This finding, in conjunction with the analyses provided in the response to the CHMP query, demonstrating efficacy of daclizumab in subjects with both highly active (approximately 40% of subjects) and less active (approximately 60% of subjects) forms of MS, demonstrated that daclizumab has efficacy across a broad spectrum of MS subjects and was considered sufficient to support an indication for “relapsing forms of MS.”

Other tertiary efficacy endpoints in Study 301 that are considered close correlates or mediators of disability progression measured by the EDSS also showed evidence of a treatment benefit of daclizumab. In Study 301, daclizumab demonstrated a benefit over IFN β-1a on physical and cognitive performance measures as defined by the MSFC composite score ($p = 0.0007$) and each of its 3 subcomponents: timed 25-foot walk ($p = 0.0060$), 9HPT ($p = 0.0016$), and the PASAT3 ($p = 0.0411$). In addition, in Study 301, daclizumab also improved cognitive function as measured by the change from baseline on the oral SDMT compared to IFN β-1a therapy at 96 weeks ($p = 0.0274$).

Treatment with daclizumab also reduced brain atrophy relative to both placebo and IFN β-1a across Studies 201/202/203 and 301, an important radiographic correlate of disability progression that may account for much of the variability in treatment effects of MS therapies on disability progression across clinical studies. The annualized PBVC in Study 301 was smaller in the daclizumab group than in the IFN β-1a group (indicating a reduction in whole brain volume loss) during baseline to Week 24 ($p = 0.0325$), a period that may reflect pseudoatrophy due to resolution of brain inflammation, as well as Week 24 to Week 96 ($p < 0.0001$), where the long-term neuroprotective effects of an MS treatment may be more accurately measured. The absolute change in whole brain volume was similar in Studies 201 and 301. In daclizumab-treated subjects, the PBVC was -0.7 during Weeks 0 to 24 in Study 301 and was -0.7 during

Weeks 0 to 52 in Study 201. During Weeks 24 to 96, the PBVC was -0.5 in daclizumab-treated subjects in Study 301 as compared to -0.6 in Year 2 in Studies 201/202. Among subjects who received 3 years of daclizumab across Studies 201/202/203, the PBVC was further reduced to -0.3 in Year 3 of daclizumab treatment, a level of whole brain volume change associated with non-MS, healthy controls of similar age.

Across the 2 pivotal studies, there was clear evidence that daclizumab reduced the physical impact of MS from the patient's perspective. The MSIS-29 physical score was assessed in both Studies 201 and 301 and demonstrated a consistent improvement in daclizumab-treated subjects as compared to no change or worsening in control subjects ($p = 0.0008$ vs. placebo in the change at 1 year in Study 201 and $p = 0.0008$ vs. IFN β-1a in the change at 2 years in Study 301). The improvement in daclizumab-treated subjects was detectable at Week 24 and then generally sustained throughout the treatment period. In both pivotal studies, daclizumab reduced the proportion of subjects with a clinically meaningful decline on the MSIS-29 physical score (≥ 7.5-point worsening from baseline). There was a 44% reduction ($p = 0.0125$) in Study 201 and a 24% reduction ($p = 0.0176$) in Study 301 in the odds of a clinically meaningful decline in the MSIS-29 physical score over the treatment period. When the treatment effect of daclizumab was assessed on the MSIS-29 psychological score and on more generic patient-reported outcome measures such as the EQ-5D, similar treatment effects were present in both pivotal studies. Overall, the consistent results on analyses of the MSIS-29 physical score supported the treatment effect of daclizumab on clinician-assessed disability progression measured by the EDSS and provided an important affirmation that the treatment benefits were meaningful to the patients.

In both trials, a sequential closed testing procedure was used to test statistical significance on secondary endpoints to protect against multiple hypothesis testing. In Study 201, lack of statistical significance on the change in the MSIS-29 Physical Impact score in the 300-mg dose group prevented testing of the MSIS-29 Physical Impact score in the 150-mg dose group within this procedure. Similarly, in Study 301, the lack of statistical significance on the 12-week confirmed disability progression analysis prevented testing of lower ranked secondary endpoints within the closed testing procedure. Nevertheless, the magnitude of the observed treatment effects on the other pre-specified secondary endpoints that were not tested as part of the sequential closed testing procedure and the similarity of the daclizumab treatment effects on these endpoints across the 201 and 301 trials make it unlikely that the results were due to chance. The consistency of the efficacy results of the 2 pivotal studies both internally with respect to the magnitude of the clinical and radiographic findings as well as the similarity of outcomes among daclizumab-treated subjects at common timepoints across the 2 studies provides strong evidence for the validity of the efficacy findings in the daclizumab development program. Substantial efforts were made in both studies to achieve and maintain effective blinding of investigators and subjects during the course of the studies. While there was potentially more opportunity for unblinding in Study 301 due to the known side effects of IFN β administration, the efficacy estimates for daclizumab were similar across clinical and radiographic endpoints, IFN-naïve and experienced patients, and those with and without flu-like symptoms during Study 301. The concordance of efficacy findings between Studies 201 and 301 on both clinical and radiologic endpoints provides further support for the integrity of the results. While the absolute rate of treatment completion was lower in the 2- to 3-year treatment period of Study 301 compared to the 1-year treatment period of Study 201, the effects of daclizumab on efficacy endpoints were observed early in treatment when the incidence of dropout was low and were then sustained throughout both studies at a similar magnitude. Sensitivity analyses that included data after treatment had been permanently discontinued and/or alternative MS treatments had been started showed similar results to the primary analyses.

In both pivotal studies, subgroup analyses of efficacy demonstrated that the effect of Daclizumab 150 mg relative to control favoured daclizumab across all key demographic and baseline characteristic subgroups for each of the efficacy endpoints analysed. There was some variation in treatment effect estimates

across the multiple subgroups analysed, but the differences between subgroups were not consistent across related efficacy endpoints. Overall, the benefits of daclizumab over the comparator group were evident in all key subgroups for each of the efficacy endpoints, and there was no convincing evidence for effect modification by any of the characteristics analysed.

2.5.3. Conclusions on the clinical efficacy

The results of the DAC HYPdaclizumab pivotal clinical studies support the following conclusions regarding the efficacy of DAC HYPdaclizumab in the treatment of subjects with relapsing forms of MS:

- Daclizumab 150 mg SC every 4 weeks produced relevant effects on clinical, radiographic, and possibly patient-reported MS outcome measures compared to both placebo and IFN β-1a, a current standard of MS care. These effects include a reduction in the risk of relapse, confirmed disability progression, number of new/newly enlarging T2 lesions, and worsening in the patient-reported physical impact of MS.
- The consistency of the efficacy results of the 2 pivotal studies supports the validity of the efficacy findings within the clinical development program.
- The efficacy of Daclizumab 150 mg was noticed within 1 month for radiographic endpoints such as new Gd-enhancing lesions, within 3 months for endpoints such as relapse, and within 6 months for disability progression.
- The effects of Daclizumab 150 mg that were observed early in treatment were sustained, over 3 years of treatment.
- The benefits of daclizumab over the comparator group were evident across prespecified subgroups defined by demographic factors and MS characteristics. There was no convincing evidence for effect modification by any prespecified characteristic.
- Overall, immunogenicity to daclizumab was typically transient and most often occurred during the first year of treatment. ABs to daclizumab had no discernible effect on clinical efficacy.
- The lowest efficacious dose of Daclizumab is 150 mg once a month by SC injection. The 300-mg dose provided no additional benefit. Doses of daclizumab lower than 150 mg may have lower efficacy and are not expected to improve tolerability based on the results of the supportive Phase 2 dose-finding study using DAC Penzberg (DAC-1012).
- The totality of the efficacy results supports the proposed commercial dose of Daclizumab 150 mg once a month that will provide clinically meaningful treatment benefits to relapsing MS patients in comparison to both placebo and IFN β-1a.

2.6. Clinical safety

The safety profile of Daclizumab has been evaluated in healthy volunteers and in MS subjects who comprise the majority of the safety data.

Safety data from the pivotal placebo-controlled Study 201 and the active-controlled Study 301 provide the best source of information defining the safety profile of daclizumab in the intended population and aid in distinguishing treatment-related events from background events expected in this population. To evaluate the long-term safety of daclizumab, safety data from the controlled studies have been combined with data from the dose-blinded and uncontrolled studies to form an integrated safety database (referred to hereafter as the total daclizumab experience).

For the 6 MS studies, the integrated safety database includes all safety data from the completed controlled and dose-blinded studies (Studies 201, 301, and 202) and safety data for the ongoing long-term extension studies as of their respective data cut-off dates (Study 203, 20 January 2014; Study 302, 03 February 2014; Study 303, 28 February 2014). Any deaths and important SAEs as of 31 October 2014 have also been described.

At the time of the data cut-offs to support the filing, 2133 MS patients have been dosed with daclizumab. Of these subjects, 348 who had previously been treated with IFN β-1a in Study 301 had received their first dose of daclizumab in Study 303 but had not had the first post-dose safety visit; therefore, they are not included in the integrated safety population.

The integrated safety population for the SCS consists of 1785 MS patients who received daclizumab for periods up to 6 years, accounting for approximately 4100 subject-years of exposure. This represents the total daclizumab experience. Of these subjects, 1215 have been exposed for ≥ 2 years and 573 were exposed for ≥ 3 years. This extent of exposure satisfies and exceeds ICH population exposure requirements for assessment of clinical safety (ICH E1).

Study data from 127 healthy volunteers from the 4 Phase 1 studies that support the development program were not integrated, since these studies are different in their design, study population, objectives, daclizumab doses, and dosing regimens. Safety results from these studies are generally consistent with the safety profile seen in the MS subjects.

During the daclizumab clinical development program, the Sponsors instituted thorough safety monitoring. Subjects had clinic visits every 4 weeks throughout the 1- to 3-year pivotal studies and every 4 to 12 weeks during the extension studies. Subjects who discontinued study treatment were encouraged to remain in the studies and to complete all follow-up study assessments, and a minimum of 6-months of safety follow-up.

An independent data safety monitoring board (DSMB) was convened to monitor safety and the overall benefit/risk profile throughout the development program, and received monthly SAE reports from all ongoing daclizumab studies, regardless of the development phase. The DSMB consisted of expert neurologists, statisticians, as well as a hepatologist, infectious disease specialist and rheumatologist/immunologist. The DSMB met regularly and evaluated AEs and SAEs, as well as laboratory data, vital signs and ECG summaries.

An increased incidence of liver transaminases and cutaneous events were observed in daclizumab clinical studies. For both observations, the Sponsor worked closely with independent expert hepatologists and dermatologists to develop detailed procedures and guidances for monitoring and managing the treatment of subjects with transaminase elevations or cutaneous events. These guidances were incorporated into the protocols and specific processes and forms for AEs of special interest were implemented in the studies to collect detailed follow-up information on hepatic and cutaneous events that occurred during treatment, enabling a comprehensive review of these events. To closely monitor the cutaneous events, a blinded, independent dermatologist (referred to hereafter as the central dermatologist) reviewed clinically significant cutaneous AEs from the ongoing studies and provided regular reports to the DSMB. A final assessment of the cutaneous safety profile of daclizumab by the central dermatologist is provided.

During Study 202, 1 subject in the Daclizumab 300 mg/washout/300 mg group died of liver failure due to autoimmune hepatitis. In response to this event and to the observed elevations in liver transaminases, all ongoing studies were updated to include liver function test (LFT) monitoring every 4 weeks during treatment if not already required, to provide additional guidelines on dose interruption and discontinuation, and to limit concomitant treatment with specific medications associated with hepatotoxicity.

An independent committee of hepatologists (the Hepatic Adjudication Committee [HAC]) was convened to better characterize the hepatic risks associated with daclizumab and to review and adjudicate specific events of hepatic injury. A summary of the key safety findings are as follows and, for brevity, are focused on the proposed dose of Daclizumab 150 mg. The safety profile for Daclizumab 150 mg and 300 mg were comparable and are discussed in the main portions of the SCS and the CSR for Study 205MS201.

Statistical Methods

Daclizumab was evaluated in 4 studies of HVs and 6 studies of subjects with MS. Data from all 6 MS studies of daclizumab, including the placebo-controlled, active-controlled, dose-blinded, and open-label studies, were used to assess the overall safety profile of daclizumab in MS subjects.

The safety assessment primarily uses analyses from the 2 pivotal studies (205MS201 and 205MS301). The distinct populations in these studies are referred to as the placebo-controlled experience and the active-controlled experience, and include all daclizumab safety data in a blinded study with a comparator (placebo or active) over a period of 1 to 3 years.

Supportive analyses were based on integrated safety data from subjects dosed with daclizumab in any of the 6 MS studies in order to summarize the overall and long-term safety experience of MS subjects who received daclizumab. This population is referred to as the total daclizumab experience.

Treatment Groups and Pooling Strategy for the Integrated Analysis of Safety

The 4 Phase 1 studies of daclizumab in HVs were neither pooled with the MS studies nor analyzed as a separate integrated group because the designs of these studies varied in the number of doses (single or multiple) and route of administration (SC or IV).

The placebo-controlled experience (Study 205MS201) and active-controlled experience (Study 205MS301) were analyzed separately. These 2 studies were not integrated into a pool of all controlled studies because of differences in treatment duration (1 year versus 2 to 3 years, respectively), uneven sample size in the common treatment 150 mg dose arm (208 vs. 919), and the absence of a common comparator.

The treatment groups in the Placebo-Controlled experience are placebo (n=204), Daclizumab 150 mg (n=208), and Daclizumab 300 mg (n=209). In most analyses of the Placebo-Controlled experience, summary statistics are presented for the combined daclizumab arms (n=417) in addition to the individual treatment groups.

The treatment groups in the Active-Controlled experience are IFN β-1a (n=922) and Daclizumab 150 mg (n=919).

The total daclizumab experience includes integrated data for subjects treated with daclizumab in any of the MS studies. The pooled treatment groups for the safety population in the total daclizumab experience are Daclizumab 150 mg (n=1492) and Daclizumab 300 mg (n=293). In all analyses of the total daclizumab experience, summary statistics are presented for the combined daclizumab arms (n=1785) in addition to the individual pooled treatment groups. Subjects randomized to Daclizumab 300 mg in Study 205MS201 or Study 205MS202 were analyzed in the Daclizumab 300 mg analysis treatment group; all others were included in the Daclizumab 150 mg analysis treatment group. Note that any subject follow-up time in Study 205MS203 for subjects in the Daclizumab 300 mg analysis treatment group remained attributed to the 300 mg dose group, even though all subjects who entered Study 205MS203 were switched to Daclizumab 150 mg at the start of that study.

Patient exposure

The placebo-controlled studies consists of data from 417 patients who received Daclizumab at 150 mg SC (n=208) or 300 mg SC (n=209), and 204 subjects who received placebo for a period of up to 1 year, representing 423 subject-years of overall exposure to Daclizumab, 211 and 212 subject-years on Daclizumab 150 mg and 300 mg, respectively.

In the active-controlled experience, 919 patients received Daclizumab 150 mg and 922 subjects received IFN β-1a for periods of up to 3 years. The mean (median) time on treatment was 100.54 (111.43) weeks for the IFN β-1a group and 102.04 (108.71) weeks for the daclizumab group. The total number of subject-years of exposure was 1872.9 years in the IFN β-1a and 1952.2 years in the daclizumab group.

For the total daclizumab experience, 1785 patients in the safety population were dosed for periods up to 6 years and the total number of subject-years exposed to daclizumab was 4098. Approximately 60% of the subjects in the total daclizumab group were exposed to at least 25 months of daclizumab.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	621	417	208	194
Active -controlled	1841	919	919	839
Open studies	1854	900	816	349
Post marketing	NA			
Compassionate use	NA			

There is a slight difference between the number of pts exposed to the proposed dose (816) and the previous value for pts exposed to the proposed dose range (831) but this may reflect the fact that some pts may have been treated with a near 150 mg dose, without a real 150 mg dose. This was not considered an issue.

Overall, the safety database is robust and sufficient for identifying uncommon risks and may also be able to detect risks with an incidence as low as 1 in 1000 subject-years associated with daclizumab.

Table 29 Treatment Groups and Pooling Strategy

Groups (n=analyzed) [N=dosed]*	Studies (duration)	Treatment regimens in the study	Treatment groups for analysis
Placebo-Controlled Experience (n=621)	Study 201 (1 year)	Placebo (n=204) DAC 150 (n=208) DAC 300 (n=209)	Placebo (n=204) DAC 150 (n=208) DAC 300 (n=209) DAC total (n=417)
Active-Controlled Experience (n=1841)	Study 301 (2-3 years)	DAC 150 (n=919) IFN (n=922)	DAC 150 (n=919) IFN (n=922)
Total DAC HYP Experience (n=1785) [N=2133] (all RRMS subjects who received DAC HYP in a controlled or uncontrolled study)	Studies 201/202/203 (ongoing)	Placebo/DAC 150/150 (n=86) DAC 150/Washout/150 (n=86) DAC 150/150/150 (n=122**) Placebo/DAC 300/150 (n=84) DAC 300/Washout/300/150 (n=88) DAC 300/300/150 (n=121**)	DAC 150 (n=1492) [N=1840] DAC 300 (n=293) DAC total (n=1785)
	Studies 301/303 (ongoing)	DAC 150 (n=919) IFN/DAC 150 (n=146) [N=494]	
	Study 302 (ongoing)	DAC 150/Washout/150 (n=113) DAC 150 (n=20, TP-DI substudy)	

201 = Study 205MS201; 202 = Study 205MS202; 202 = Study 205MS202; 301= Study 205MS301; 302 = Study 205MS302; 303 = Study 205MS303; IFN = interferon; TP-DI = therapeutic protein-drug interaction

* N dosed is displayed if different from analyzed safety population. For subjects receiving DAC HYP for the first time in Study 303, some post-dosing follow-up was required for inclusion in the safety population (see Section 1.1.4.2) prior to the data cut-off. Study 303 was still enrolling at the time of the data cut-off.

** Includes Study 201 DAC HYP subjects who did not enter Study 202.

Adverse events

The safety results in this section are presented for the placebo-controlled daclizumab experience (Study 205MS201, 1 year of exposure), the active-controlled daclizumab experience (Study 205MS301, 2 to 3 years of exposure), and the total daclizumab experience for controlled and uncontrolled studies (up to 6 years of daclizumab exposure). The placebo-controlled, active controlled and total daclizumab analyses included all available information from the first dose of treatment up to 180 days after the last dose of any study treatment in the subject's last study, regardless of whether the subject received alternative MS therapy. All AE analyses in this section are presented according to the principle of treatment emergence.

Placebo-Controlled Experience

- In Study 205MS201, the overall incidence of AEs was similar across groups (79% placebo, 73% and 76% in the Daclizumab 150 mg and 300 mg groups, respectively). The majority of subjects had AEs that were mild or moderate in severity. The incidence of subjects with severe AEs was 3% in the placebo group, 4% in the Daclizumab 150 mg group, and 6% in the Daclizumab 300 mg group. The incidence of subjects with treatment-related AEs was higher in the daclizumab group than in the placebo group (22% placebo, 29% Daclizumab 150 mg, 35% Daclizumab 300 mg).

The incidence of SAEs was higher in the placebo group (26%) than in the Daclizumab groups (15% Daclizumab 150 mg, 17% Daclizumab 300 mg) due to the higher incidence of MS relapse in the placebo group. The incidence of SAEs excluding MS relapse was higher in Daclizumab 300 mg group (9%) and similar in the placebo and Daclizumab 150 mg groups (6% and 7%, respectively). The incidence of AEs leading to treatment discontinuation was higher in the Daclizumab groups (3% Daclizumab 150 mg, 4% Daclizumab 300 mg) compared with placebo (<1%).

Active-Controlled Experience

- In Study 205MS301, the overall incidence of AEs was balanced across the 2 treatment groups (91% IFN β-1a, 91% Daclizumab). The incidence of AEs that were considered severe was 14% in the Daclizumab group and 12% in the IFN β-1a group. More subjects in the IFN β-1a group (65%) than in the daclizumab group (52%) had AEs that were considered by the Investigator to be related to study treatment. Excluding MS relapse, there was a higher incidence of SAEs and AEs leading to study treatment discontinuation in the daclizumab group compared with the IFN β-1a group (SAEs: 10% IFN β-1a, 15% daclizumab; AEs leading to discontinuation: 9% IFN β-1a, 14% daclizumab). The incidence of withdrawal from study due to AEs was similar for the 2 groups (7% in each group).

Total daclizumab Experience

- The overall incidence of AEs for all subjects who received daclizumab in the total daclizumab experience was 88%. In general, the incidence of subjects with AEs, moderate or severe AEs, AEs related to study treatment, and SAEs and AEs leading to study discontinuation in the total daclizumab experience was similar to the placebo- and active-controlled experiences.

Overall Incidence of Adverse Events

In the total daclizumab group, the most common AEs (≥ 20%) by SOC were infections and infestations (62%), nervous systems disorders (50%), skin and subcutaneous tissue disorders (35%), general disorders and administration site conditions (31%), gastrointestinal disorders (26%), musculoskeletal and connective tissue disorders (26%), and investigations (24%). The most common AEs (incidence ≥ 10%) in total daclizumab group are multiple sclerosis relapse, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection.

Table 30 Adverse Reactions Reported for daclizumab

System Organ Class	Adverse Reaction	Frequency
Infections and Infestations	Nasopharyngitis†	Very common
	Upper respiratory tract infection†	Very common
	Influenza†	Common
	Bronchitis	Common
	Pharyngitis	Common
	Respiratory tract infection	Common
	Tonsillitis†	Common
	Rhinitis*	Common
	Viral infection	Common
	Pneumonia	Common
	Laryngitis	Common
	Folliculitis	Common
Blood and lymphatic system disorders	Lymphadenopathy†	Common
	Anaemia*	Common
	Lymphadenitis	Common
Psychiatric disorders	Depression*	Common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain†	Common
Gastrointestinal disorders	Diarrhea	Common
Skin and subcutaneous tissue disorders	Rash*†	Common
	Eczema†	Common
	Erythema	Common
	Pruritus	Common
	Acne†	Common
	Seborrhoeic dermatitis†	Common
	Dry skin	Common
	Dermatitis	Common
	Dermatitis allergic	Common
	Rash maculopapular	Common
	Psoriasis	Common
	Skin exfoliation	Common
	Exfoliative rash	Uncommon
	Eczema nummular	Uncommon
	Toxic skin eruption	Uncommon
General disorders and administration site conditions	Pyrexia*	Common
Investigations	ALT increased*	Common
	AST increased*	Common
	Liver function test abnormal	Common
	Hepatic enzyme increased	Common

*Observed with a ≥2% higher incidence than placebo.
†Observed with a ≥2% higher incidence than IFN β-1a IM.

Regarding suicidal behaviour in study 201: there were no serious events related to suicidal behaviour (completed suicide, attempted suicide, or suicidal ideation). However, there was an imbalance in adverse events related to depression and depressed mood in subjects treated with daclizumab in Study 201. All events were mild or moderate in intensity and no subject discontinued study drug for depressive adverse

events. In Study 201 and Study 205MS301, concomitant use of antidepressant / anxiolytic / antipsychotic medications was balanced across treatment arms. For these analyses, medications were identified using the ATC codes as designated in the WHO Drug Dictionary and included all drug codes that were assigned ATC code N06A ANTIDEPRESSANTS, NO5B ANXIOLYTICS and NO5A ANTIPSYCHOTICS for antidepressants, anxiolytics and antipsychotic medications, respectively, as well as the corresponding ATC codes that roll up to each of those classes.

Serious adverse events and deaths

Deaths

As of 31 October 2014, 10 deaths have been reported in the daclizumab clinical development program. Five deaths were reported among the 922 subjects who had received IFN β-1a, and 5 were reported among 2133 subjects who had received daclizumab. There were no deaths reported in the HV studies.

Seven subjects died while on study and are listed in Appendix Table 43. Two subjects (3011291 and 3010274) died after withdrawing from the study, and 1 subject (3010977) died after the data cut-off date. A summary of all deaths is provided in Table below. Of the 5 deaths that occurred during or after treatment with daclizumab, there were 2 cases in which a contributory role for daclizumab could not be excluded. In Study 205MS201, 1 subject who was treated with Daclizumab 150 mg and was recovering from a serious rash died due to ischemic colitis that occurred secondary to a psoas abscess. In Study 205MS202, 1 subject in the Daclizumab 300 mg/washout/ 300 mg reinitiation group died of liver failure due to autoimmune hepatitis. In the other 3 cases that occurred during or after treatment with daclizumab, death was not considered related to study treatment. In subjects treated with IFN β-1a in Study 205MS301, there were 4 deaths secondary to acute myocardial infarction, peritonitis, completed suicide, and metastatic cancer of the pancreas. After discontinuing from the study, 1 subject died from MS progression. None of the deaths were considered related to study treatment.

Table 31 Listing of Deaths

Treatment Group	Subject No.	Age, Sex, Country	Study Day of Death	Cause of Death	Relationship of Death to Study Treatment	Risk Factors or Relevant Medical History
Study 205MS201						
DAC HYP 150 mg	2010516	49-year-old, female, United Kingdom	402	Colitis ischemic and psoas abscess	Related	The subject had a complex clinical course beginning with hospitalization for a maculopapular rash.
Study 205MS202						
DAC HYP 300 mg/ washout/300mg	2010177	45-year-old, female, Ukraine	692 (Day 315 of Study 202)	Autoimmune hepatitis liver failure, multiple organ failure	Not related	None
Study 205MS301						
IFN β-1a	3010469	40-year-old, male, Russian Federation	145	Acute myocardial infarction	Not related	This subject had a medical history that included hypertensive disease, acute myocardial infarction, coronary disease, atherosclerosis of aorta, and coronary stenting.
	3011419	43-year-old, female, Russian Federation	148	Peritonitis	Not related	This subject developed peritonitis after an emergency laparotomy for abdominal pain.
	3011007	41-year-old, male, Ukraine	446	Suicide	Not related	None
	3010181	53-year-old, male, Czech Republic	924	Pancreatic cancer metastatic	Not related	This subject had neuropathic pain and was hospitalized. CT scan showed tumorous process in the left lung, tumorous enlargement of the pancreas, and metastatic process in the liver.
	3011291	28-year-old, male, India	284	Progressive relapsing MS	Not related	None
DAC HYP 150 mg	3010178	46-year-old, female, India	202	Multiple sclerosis, pneumonia aspiration, decubitus ulcer, sepsis, cardio-respiratory arrest	Not related	This subject developed acute exacerbation of MS that involved the brainstem and lost her ability to swallow.
	3010274	37-year-old, female, India	179	Acute respiratory distress syndrome, septic shock	Not related	This subject developed an acute exacerbation of MS that involved the brain stem.
Study 205MS303						
DAC HYP 150 mg	3010977	39-year-old, female, Russian Federation	193	Subdural haematoma, brain oedema, brain compression, traumatic intracranial haemorrhage	Not related	This subject fell in the bathroom and developed compression of ventricular system and large traumatic subarachnoid hemorrhage that led to brain edema and dislocation.

Sources: Individual Subject narratives in the respective CSRs and in Appendix Table 43 for 7 subjects who died on study. For 3 subjects (3011291 and 3010274, who died after leaving the study, and 3010977, who died after the data cut-off date), the Investigators reported the deaths to the Sponsor through the adverse event reporting system.

Other Serious Adverse Events

SAEs are described in this section for the placebo-controlled, active-controlled, and total daclizumab experiences.

Placebo-Controlled Experience

In Study 205MS201, the incidence of SAEs was 26%, 15%, and 17% in the placebo, Daclizumab 150 mg, and Daclizumab 300 mg groups, respectively. Excluding MS relapse, the incidence of SAEs was 6%, 7%, and 9% in the placebo, Daclizumab 150 mg, and Daclizumab 300 mg groups, respectively. The most common SAEs by SOC (≥ 1% in any treatment group) were nervous system disorders, infections and infestations, skin and subcutaneous disorders, and gastrointestinal events . The most common SAE by PT was MS relapse (22% placebo, 9% Daclizumab 150 mg, 9% Daclizumab 300 mg). All other SAEs by PT occurred in <1% of subjects each, and none occurred in more than 1 subject in any group. The

percentage of subjects reporting an SAE in each 3-month interval was consistent across the duration of the study, indicating no overall time-related pattern of reporting of SAEs.

Active-Controlled Experience

In Study 205MS301, the incidence of SAEs was higher in the daclizumab group than in the IFN β-1a group (24% vs. 21%, respectively). Excluding MS relapse, SAEs were reported in 10% of the IFN β-1a group and 15% of the daclizumab group. In the daclizumab group, SOCs with an incidence of SAEs ≥ 1% were nervous system disorders (12%); infections and infestations (4%); neoplasms, benign, malignant, and unspecified and skin and subcutaneous disorders (2% each); and blood and lymphatic system disorders and gastrointestinal disorders (1% each). SAEs reported in 3 or more daclizumab-treated subjects were MS relapse, urinary tract infection, pneumonia, lymphadenopathy, convulsion, fall, uterine leiomyoma, lymphadenitis, depression, dermatitis, and nephrolithiasis. With the exception of MS relapse, all of these SAEs were reported in <1% of subjects. In the IFN β-1a group, SOCs with an incidence of SAEs ≥ 1% were nervous system disorders (14%); infections and infestations (2%); and neoplasms, benign, malignant, and unspecified (1%). SAEs reported in 3 or more subjects in the IFN β-1a group were MS relapse, acute myocardial infarction, cholelithiasis, and ectopic pregnancy. With exception of MS relapse, all these SAEs were reported in <1% of subjects. In the active-controlled experience, to evaluate potential for atypical MS relapse, a search for SAEs of MS relapse considered related to study treatment and for verbatim terms of "atypical MS relapse" were performed. Based on this search and subsequent medical review, there were no confirmed events of atypical MS in the daclizumab group.

Total daclizumab Experience

In the total daclizumab experience, the overall incidence of SAEs was 25%; excluding MS relapse, the incidence of SAEs was 16%. The SOCs with the highest incidence of SAEs was nervous system disorders (13%). Excluding nervous system disorders, SOCs with the highest incidence (≥ 1%) of SAEs in the total daclizumab group were infections and infestations (4%); skin and subcutaneous tissue disorders (2%); gastrointestinal disorders (2%); neoplasms benign, malignant and unspecified: injury, poisoning, and procedural complications; and blood and lymphatic disorders (1% each). In the total daclizumab experience, other SAEs occurring in 3 or more subjects are described in Table 32. SAEs occurring in 5 or more subjects were MS relapse, pneumonia, urinary tract infection, lymphadenopathy, bronchitis, colitis ulcerative, hepatic enzyme increased, MS, and ovarian cyst. With the exception of MS relapse, all of these SAEs were reported in <1% of subjects.

Table 32 Serious Adverse Events Occurring in 3 or More Subjects

	DAC HYP 150 mg	DAC HYP 300 mg	Total DAC HYP
Number of subjects in the pooled safety population	1492 (100)	293 (100)	1785 (100)
Number of subjects with a serious event	345 (23)	102 (35)	447 (25)
MULTIPLE SCLEROSIS RELAPSE	155 (10)	54 (18)	209 (12)
PNEUMONIA	10 (<1)	2 (<1)	12 (<1)
URINARY TRACT INFECTION	11 (<1)	1 (<1)	12 (<1)
LYMPHADENOPATHY	5 (<1)	3 (1)	8 (<1)
BRONCHITIS	1 (<1)	4 (1)	5 (<1)
COLITIS ULCERATIVE	4 (<1)	1 (<1)	5 (<1)
HEPATIC ENZYME INCREASED	3 (<1)	2 (<1)	5 (<1)
MULTIPLE SCLEROSIS	4 (<1)	1 (<1)	5 (<1)
OVARIAN CYST	3 (<1)	2 (<1)	5 (<1)
APPENDICITIS	4 (<1)	0	4 (<1)
CONVULSION	4 (<1)	0	4 (<1)
FALL	4 (<1)	0	4 (<1)
HEPATITIS TOXIC	4 (<1)	0	4 (<1)
LYMPHADENITIS	4 (<1)	0	4 (<1)
NEPHROLITHIASIS	3 (<1)	1 (<1)	4 (<1)
ABORTION SPONTANEOUS	3 (<1)	0	3 (<1)
ADENOMYOSIS	2 (<1)	1 (<1)	3 (<1)
AUTOIMMUNE HEPATITIS	1 (<1)	2 (<1)	3 (<1)
CELLULITIS	3 (<1)	0	3 (<1)
DEPRESSION	3 (<1)	0	3 (<1)
DERMATITIS	3 (<1)	0	3 (<1)
DRUG HYPERSENSITIVITY	2 (<1)	1 (<1)	3 (<1)
ENDOMETRIOSIS	3 (<1)	0	3 (<1)
PULMONARY EMBOLISM	2 (<1)	1 (<1)	3 (<1)
URTICARIA	2 (<1)	1 (<1)	3 (<1)
UTERINE LEIOMYOMA	3 (<1)	0	3 (<1)
VIRAL INFECTION	3 (<1)	0	3 (<1)

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 total column.

SOURCE: DACMS/BLA/BLA/T-AE-SER-PT-GE3SUBJ.SAS DATE: 29SEP2014

Upon request, the applicant performed a medical review of all available documentation which indicated that there were 11 subjects with severe depression, 9 of the 11 subjects had a history of depression prior to exposure to daclizumab. There were 7 suicide attempts in 6 subjects who were being treated with daclizumab and 2 of the subjects who attempted suicide had no prior history of depression.

In summary,

- Study 201 shows that daclizumab has an imbalance in depression events, favouring placebo. No events related to suicidality were reported in this study.
- Study 301 shows similar rates of depression events compared to IFN β-1a. The one completed suicide occurred in a subject treated with IFN β-1a. Suicidal ideation was balanced (2 daclizumab; 2 IFN β-1a), 2 subjects attempted suicide in IFN β-1a vs none in daclizumab, and there is one event of depression suicidal in daclizumab vs. none in IFN β-1a.
- On comprehensive review of all information available, across all studies, 6 subjects being treated with daclizumab attempted suicide. Two of these did not have a prior history of depression.

The applicant has acknowledged that Suicidal related behaviour is an important identified concern and that DAC may be related to an increase in the severity of this symptomatology, already frequent in MS. The applicant has upgraded depression in RMP to an important identified risk, and also proposes new wording to SmPC sections 4.4 as further measure for risk minimisation:

“Depression
Zinbryta should be administered with caution to patients with previous or current depressive disorders. Patients treated with Zinbryta should be advised to report any symptoms of new or worsening depression, and/or suicidal ideation to the prescribing physician. If a patient develops severe depression, and/or suicidal ideation, discontinuation of Zinbryta should be considered (see section 4.8).” These measures may be appropriate to minimise risk.

Laboratory findings

Hematology Results

Summary of hematology results:

- No clinically significant changes from baseline in aggregate haematological values were observed across treatment groups. However in the overall daclizumab group, the incidence of decreased post-baseline CD4+ (<400 cells/µL, <200 cells/µL) was 29% and 3%, respectively, and the incidence of decreased CD8+ counts (<200 cells/mm3, <100 cells/mm3) was 34% and 4%, respectively.

Blood Chemistry Results

Summary of blood chemistry results:

- With the exception of liver function tests, no treatment-related differences were noted in subjects treated with daclizumab compared to placebo or IFN β-1a.
- Laboratory results pertaining to liver function showed a higher incidence of elevations in transaminases in subjects treated with daclizumab than in subjects treated with placebo or IFN β-1a.

Liver Function Tests

In the total daclizumab population, the majority of subjects who experienced elevated transaminases (ALT or AST) had maximum post-baseline values <3×ULN. ALT or AST elevations >1×ULN at any time during the study occurred in 47% of daclizumab-treated subjects, elevations ≥ 3×ULN occurred in 11% of subjects, and elevations >5×ULN occurred in 6% of subjects. The incidence of ALT or AST elevations was consistent over time when measured by 6-month intervals.

Kidney Function

In the total daclizumab experience, shifts to high BUN or creatinine values occurred in ≤ 5% of subjects, and shifts to low were observed for creatinine in 1 subject and for BUN in 3 subjects. Mean values from baseline for BUN and creatinine remained stable throughout the study and showed no clinically relevant changes over time. Mean changes from baseline for BUN and creatinine were variable over time. The percentage increase from baseline after Week 48 for BUN and remained stable over time for creatinine. None of these changes were clinically relevant over time.

Urinalysis Results

In the total daclizumab experience, the incidences of shift to high/positive test results for all urinalysis parameters did not reveal any consistent pattern in the development of abnormalities.

Other Laboratory Test Results

In Study 205MS301, no clinically significant changes were observed for thyroid function across treatment groups. Shifts to high TSH and to low thyroxine were similar in the 2 treatment groups and occurred in ≤ 5% and ≤ 12% of subjects, respectively. Shifts to low TSH and to high thyroxine occurred in ≤ 8% and ≤

6% of subjects, respectively (CSR 205MS301, Table 55). Mean values and mean changes from baseline for TSH and total thyroxine remained stable throughout the study in both treatment groups and showed no clinically relevant changes over time; mean values were within the normal range at all timepoints during the study.

Vital Signs

Similar to the placebo- and active-controlled experiences, there were no clinically significant changes in vital signs from baseline to the end of treatment observed in the total daclizumab experience. Overall, the incidence of abnormal post-baseline vital signs and changes in vital signs from baseline using different criteria was comparable to the active-controlled experience, and no clinically relevant changes were noted.

Electrocardiogram

In the total daclizumab experience, ECG results were similar to the results from the placebo- and active-controlled experiences. The absolute values and changes in time from baseline by visit for ECG quantitative parameters (heart rate, PR interval, QRS interval, QT interval, QTcF interval, QTcB interval) showed no clinically significant changes.

Beck Depression Inventory, Second Edition

In the active-controlled experience (Study 205MS301), the results of the BDI-II showed no clinically meaningful differences between the 2 treatment groups, nor were there any clinically meaningful changes from baseline over time (CSR 205MS301, Table 335). Daclizumab-treated subjects had greater improvement on the MSIS-29 Psychological Impact score compared with the IFN β-1a group.

Immunogenicity Analyses

Subjects who were evaluated for immunogenicity were required to have at least 1 post-baseline immunogenicity test. Immunogenicity was determined by measuring anti-drug antibodies (ADAs) using validated assays. Samples that generated a positive response for ADA were further tested for the presence of neutralizing antibodies (NAbs).

Several analyses were performed to detect the impact of ADAs and NAbs on the safety profile of daclizumab for subjects who received Daclizumab 150 mg or 300 mg.

Results show that most ADA and NAb reactivity to daclizumab occurred early during treatment, and that this reactivity was transient. Also, the ADA titers observed were generally low. There was no discernible impact of immunogenicity status on the efficacy, PK, or PD profile of daclizumab. The immunogenicity data with 150 mg and 300 mg doses of daclizumab pooled from all clinical studies were used to summarize key safety parameters by antibody status to see whether there was any impact of ADAs and/or NAbs on the safety profile of daclizumab.

Safety in special populations

Adverse events were examined by the intrinsic factor subgroups of age, gender, race, and body weight, and the extrinsic factors of study region (based on geography and health care systems), prior MS treatment history, alcohol use, smoking status, and antibody status. Overall, although some differences in the incidence of AEs by age and race and by region were observed, there were no clinically relevant differences for these factors, and no impact on the use of daclizumab is expected. There were no significant clinically relevant differences in the safety profile of daclizumab in subjects with and without

prior DMTs (ABCR or immunomodulatory therapy). The available data were evaluated in the following special populations:

- Safety With Use of Systemic Steroids
- Effects on Influenza Vaccine Protection
- Pregnancy, Reproduction, and Lactation
- Pediatric and Elderly Populations
- Hepatic and Renal Impairment
- Overdose and drug abuse

No special safety concern was identified de novo, but it confirmed previous signals, such as hepatic failure risk.

Immunological events

Several analyses were performed to evaluate the impact of ADAs and NAbs on the safety profile of daclizumab for all evaluable subjects who received daclizumab (either 150 mg or 300 mg). There was no correlation with AEs or SAEs based on antibody-positive or -negative status for either ADAs or NAbs. Also, there was no pattern of association between antibody status and anaphylaxis/ hypersensitivity type events. These results suggest that ADAs or NAbs had no discernible effect on the safety profile of daclizumab.

- Anaphylaxis and hypersensitivity
- Autoimmune disorders

Safety related to drug-drug interactions and other interactions

A Therapeutic Protein-Drug Interaction (TP-DI) substudy showed that daclizumab did not affect the systemic exposure of concomitantly administered probe drugs for CYP isoenzymes. In addition, no safety signal of daclizumab related to concomitant IV treatment with corticosteroids was identified.

Interaction with antispastic agents or fampridine has not been discussed at MA submission. Upon request the applicant performed an analysis which did not find any relation suggesting a DDI. The applicant did not perform drug-drug specific trials. All data available for analysis came from efficacy trials. DAC is a monoclonal antibody which does not affect directly other frequently used concomitant treatments which include baclophen, diazepam / tetrazepam, tizanidine and tolperisone. As for fampridine, of all patients enrolled, only 15 were concomitantly treated with daclizumab and fampridine. Evaluation of the AE profile of each DAC-other agent combination did not reveal any discrepancy when compared to DAC alone + other agent alone. Considering that from a pharmacological point of view it is also not expected that interactions may occur on a clinically relevant level, the applicant explanation may be accepted.

Discontinuation due to AES

In the total daclizumab experience, the overall incidence of AEs that led to discontinuation of study treatment was 14%. SOCs with incidence ≥ 1% of AEs by SOC leading to study treatment discontinuation in the total daclizumab group were skin and subcutaneous tissue disorders (4%), investigations (4%) and nervous system disorders (1%). AEs by PT that led to treatment discontinuation in ≥ 1% of subjects in the

total daclizumab experience were ALT increased (2%), LFT abnormal (1%), and MS relapse (1%). The incidence of AEs that led to treatment discontinuation remained stable over time, ranging from 4% to 6% per year.

In the total daclizumab experience, the incidence of AEs that led to withdrawal from study was 9%. In general, the pattern of AEs leading to withdrawal from the study was similar to that observed for AEs leading to discontinuation of study treatment. The most common AEs by SOC leading to study withdrawal are investigations (3%) and skin and subcutaneous tissue disorders (2%). AEs by PT that led to withdrawal from study in ≥ 1% of subjects included ALT increased (1%).

2.6.1. Discussion on clinical safety

The safety of Daclizumab 150 mg has been characterized in clinical studies of 1785 MS subjects treated for up to 6 years, accounting for approximately 4100 subject-years of exposure. During the accumulation of this safety data, several important risks have emerged, including elevations of liver transaminases and hepatic injury, cutaneous events, infections, depression and colitis and strategies and approaches to monitor and mitigate these risks have been implemented and tested in the clinical studies.

daclizumab is associated with a risk of elevations of serum transaminases and cases of hepatic injury. Most often this risk manifests as a transient and asymptomatic increase in ALT/AST that resolves spontaneously or with discontinuation of dosing. In a small number of cases, serious events of hepatic injury, characterized by concomitant elevations of serum transaminases and bilirubin, were identified in which daclizumab may have played at least a significant contributory role based on independent adjudication of the events. With the exception of a fatal case of autoimmune hepatitis early in the clinical development program, prompt identification of these cases, discontinuation of daclizumab, and treatment of underlying or other contributory causes resulted in favourable outcomes. While a single dose of daclizumab given at the time of a transaminase abnormality generally did not appear to worsen or prolong events, the single case of fatal autoimmune hepatitis occurred in the setting of repeated administration of daclizumab during the elevation. Treatment discontinuation for patients meeting certain criteria (and possibly for others, based on physician judgment) is appropriate to limit the severity of the event and to reduce the risk of recurrence in susceptible individuals. The most common cutaneous events during daclizumab use were dermatitis, eczema, and rashes, which were manageable with treatment, including topical and/or systemic steroids, and treatment discontinuation. Some cases were serious and had features of a delayed-type hypersensitivity reaction. These cases typically presented with a more generalized, diffuse rash, and some cases required multiple courses of corticosteroids. While the most serious cases could be a source of significant discomfort to patients, the integrity of the skin was preserved and none of the events were directly life-threatening. Overall, the use of corticosteroids appeared to result in rapid improvement of many of the more serious cases. Over time, events generally resolved or substantially improved without permanent injury to the skin.

Infections were composed mainly of upper respiratory tract, urinary tract, and viral infections typical of those seen in a non-immunocompromised MS population. While the incidence of both minor and serious infections was increased during daclizumab use, the pattern and outcome of the events indicated that the ability of the subjects' immune system to effectively respond to the infection was preserved. Overall, the infections that have occurred during daclizumab use have been manageable with standard care, and the incidence of infections necessitating discontinuation of study treatment has been <1%.

Serious cases of colitis characterized by prolonged diarrhoea, fever, and abdominal pain have been reported in <1% of subjects treated with daclizumab. These events have had a late onset, occurring after 1 year of treatment. These cases had features different from Crohn's disease and did not progress to have

any of the serious sequelae of chronic inflammation, such as perforation, fistulas, or abscess formation. The events appeared to be limited and were managed by discontinuation of study treatment and by standard treatment with anti-inflammatory agents and steroids.

Overall, the safety profile of daclizumab includes several serious risks, including elevations of serum transaminases and hepatic injury, cutaneous events, infections, and colitis. Based on the known immunomodulatory effect of daclizumab and the pattern of AEs observed, including response to treatment, an immune-mediated mechanism was implicated in some of these events. During the development program, procedures were developed in conjunction with experts to enable early identification and management of these risks, and were tested during the clinical studies. These procedures can be translated into the clinical setting and used to provide guidance to prescribers. With appropriate physician and patient education and clinical vigilance, the risks associated with daclizumab can be managed by awareness and early recognition of developing risks, standard medical care, and treatment discontinuation.

There was one death following re-introduction of treatment with daclizumab in Study 205MS202. The Applicant proposed monthly monitoring of liver enzymes in patients treated with daclizumab. The Applicant has engaged a panel of independent expert hepatologists (the Hepatic Adjudication Committee; [HAC]) to adjudicate hepatic events. In the course of their duties, we have requested that the HAC review the proposed monitoring, treatment suspension, and discontinuation rules. The HAC endorsed the measures implemented in the protocols. The HAC was generally in agreement with the proposed recommendation in Section 4.4 of the Summary of Product Characteristics (SmPC) except that it felt that >3×ULN for transaminases was too low a threshold to hold dose, preferring 5× or 8×ULN (HAC 29/30 July 2014 minutes). Overall a conservative approach for treatment discontinuation (ALT or AST >5×ULN), treatment suspension (ALT or AST >3×ULN), and treatment resumption (ALT or AST <2×ULN) was adopted as described below, given its success in the clinical program. After D120 quest, the applicant revised the criteria, and maintains its position to consider that the original proposal that daclizumab dosing be held until the transaminases return to <2 x ULN is still appropriate. Considering that the risk of relapse if a patient stops skips one treatment or two at the most is at the verge of increasing the risk of relapse (which usually increases between the 4th and the 6th month, then reaching baseline levels), there is a time window where DAC may be stopped for safety reasons without jeopardising much efficacy.

2.6.2. Conclusions on the clinical safety

The safety database for daclizumab is sufficiently robust, with 2133 subjects with RMS who have received daclizumab. Of these, 348 subjects are not included in the safety population because they received their first dose of daclizumab in Study 205MS303, but had not yet had the first post-dosing safety visit at the time of database cut-off. The safety population includes 1785 subjects exposed to daclizumab for periods of up to 6 years, accounting for approximately 4100 subject-years. Of these, 1215 subjects were exposed for ≥ 2 years and 573 subjects for ≥ 3 years at or above the proposed commercial dose of 150 mg daclizumab. Thus, the safety database is sufficient for identifying uncommon risks and may also be able to detect risks associated with daclizumab with an incidence as low as 1 in 1000 subject-years.

The overall incidence of AEs was balanced in the placebo-controlled (79% placebo, 73% Daclizumab 150 mg) and active-controlled (91% IFN β-1a, 91% Daclizumab 150 mg) pivotal studies. The majority of subjects had events that were mild to moderate in severity. A higher incidence of severe events was seen in daclizumab treated subjects in the placebo-controlled (3% placebo, 4% Daclizumab 150 mg) and active-controlled (12% IFN β-1a, 14% daclizumab) studies.

There was an increased incidence of serious events excluding MS relapse in the daclizumab-treated subjects in the placebo-controlled (6% placebo, 7% daclizumab 150 mg) and active-controlled (10% IFN β-1a, 15% Daclizumab 150 mg) experience. In the placebo-controlled experience, the most common SAEs (≥ 1%) by SOC in the Daclizumab 150 mg group were nervous system disorders (10%), infections and infestations (3%), and gastrointestinal (GI) disorders (1%). In the active-controlled experience, the most common SAEs (≥ 1%) by SOC in the daclizumab group were nervous system disorders (12%); infections and infestations (4%); neoplasms, benign, malignant, and unspecified and skin and subcutaneous disorders (2% each); blood and lymphatic system disorders and GI disorders (1% each). Most of the increased incidence in serious events for daclizumab-treated subjects was attributable to a small incremental increase of 1% to 2% in serious infections and serious cutaneous events.

The most common (≥ 5%) adverse drug reactions (ADRs) reported at an increased incidence (≥ 2%) in subjects treated with daclizumab compared with placebo were upper respiratory tract infection, rash, depression, and ALT increased. The most common ADRs (≥ 5%) reported at an increased incidence (≥ 2%) in subjects treated with daclizumab compared with IFN β-1a were nasopharyngitis, upper respiratory tract infection, influenza, oropharyngeal pain, rash, and lymphadenopathy.

As of October 31 2014, 10 deaths were reported in the clinical development program, including 5 of 922 subjects who received IFN β-1a (acute myocardial infarction, peritonitis, suicide, metastatic pancreatic cancer, and progressive relapsing MS) and 5 of 2133 subjects who received daclizumab (ischemic colitis; autoimmune hepatitis; complications of brainstem lesions of MS in 2 subjects; trauma and acute subdural hematoma). In 2 cases (ischemic colitis, autoimmune hepatitis), a contributory role for daclizumab could not be excluded. None of the other deaths were considered related to study treatment, including one suicide event.

There was an increased incidence of hepatic events and transaminase elevations in subjects treated with daclizumab.

Compared with placebo and IFN β-1a, an increased incidence of infections (44% placebo vs. 50% Daclizumab 150 mg; 57% IFN β-1a vs. 65% Daclizumab 150 mg) and serious infections (0% placebo vs. 3% Daclizumab 150 mg; 2% IFN β-1a vs. 4% Daclizumab 150 mg) was observed in subjects who received daclizumab. The most common infections by high-level term (HLT) in daclizumab-treated subjects were upper respiratory tract infections, urinary tract infections, and viral infections. The time to onset, median duration, and percentage of infections that resolved were similar between the daclizumab and either placebo or IFN β-1a groups. The overall rate of infections and serious infections did not increase over time. The majority of subjects with infections continued on study treatment, and discontinuations due to infection were <1% for all daclizumab-treated subjects. The pattern and type of infections observed was consistent with those seen in the MS population and was not representative of the types of infections characteristically seen in immunocompromised or immunosuppressed populations.

Cutaneous events (13% placebo vs. 18% daclizumab 150 mg; 19% IFN β-1a vs. 37% Daclizumab 150 mg) and serious cutaneous events (0% placebo vs. <1% Daclizumab 150 mg; <1% IFN β-1a vs. 2% Daclizumab 150 mg) were increased in subjects who received daclizumab compared with those who received placebo or IFN β-1a. The most common cutaneous events in daclizumab-treated subjects were rash, dermatitis, and eczema. The majority of cutaneous events were mild or moderate in severity; 2% of subjects had severe events. Overall, 4% of subjects discontinued daclizumab due to cutaneous events. Most events resolved following treatment with topical or systemic corticosteroids.

Gastrointestinal (GI) events in the GI SOC were reported by more daclizumab-treated subjects in the placebo-controlled (11% placebo vs. 16% Daclizumab 150 mg) and active-controlled (24% IFN β-1a vs. 31% Daclizumab 150 mg) experiences. The majority of subjects with GI events had events that were mild

or moderate in severity. Diarrhea was the most commonly reported GI event. In general, events of diarrhea were similar in incidence, median duration, and percentage of events resolved across the IFN β-1a and daclizumab groups. There was an increased incidence of prolonged diarrhea (>3 weeks) in daclizumab-treated subjects compared with the IFN β-1a treated subjects.

In the total daclizumab experience, 1 out of 1785 subjects (0.06%) had an SAE of potential anaphylaxis (reported with a preferred term of circulatory collapse) that was characterized by dizziness, hypotension, and syncope after the first dose of daclizumab. The event was not life-threatening and the subject was treated with IV fluids and prednisone. In the active-controlled experience, 1 of 922 subjects (0.11%) in the IFN β-1a group and 0 subjects in the daclizumab group had an anaphylactic reaction. Analyses of AEs and SAEs within 24 hours of an injection, of SAEs during the first 6 injections, and of SAEs after discontinuation and reinitiation of treatment showed no other events of anaphylaxis.

In the daclizumab-treated subjects, there was a higher incidence of AEs in the hypersensitivity SMQ and allergic conditions HLGT than in placebo or IFN β-1a subjects. However, this difference was due primarily to an increase of events in the skin and subcutaneous tissue disorders SOC and was not consistent with anaphylaxis or immediated-type drug hypersensitivity events. In the opinion of the central dermatologist, the majority of cutaneous reactions appeared to be eczematous or psoriatic in nature or typical of normal conditions seen in a dermatology practice, with a small number of events characterized as delayed-type drug hypersensitivities.

The incidence of potential autoimmune disorders based on pre-specified terms was similar in the placebo-controlled (0% placebo vs. <1% Daclizumab 150 mg) and active-controlled (<1% IFN β-1a vs. 1% Daclizumab 150 mg) experiences. Events representing autoimmune thyroiditis were most common, and the incidence in daclizumab-treated subjects was similar to that observed in the MS population. The incidence of serious events was <1%, and there was no pattern to the events. Based on the limited number of events, there does not appear to be an association between daclizumab and potential autoimmune events.

There was an increased incidence of lymphadenopathy and lymphadenitis in subjects treated with daclizumab. The majority of subjects were asymptomatic. In cases in which biopsies were taken, the results were consistent with a reactive or inflammatory process, and there was no evidence of malignancy.

The incidence of depression was evaluated using the prespecified SMQ of depression and suicide/self-injury. In the placebo-controlled experience, events from the SMQ were reported at a higher incidence in daclizumab-treated subjects (3% placebo vs. 7% Daclizumab 150 mg), with no suicidal ideation, severe events, serious events, or events leading to treatment discontinuation reported in subjects who received daclizumab. In the active-controlled experience, the overall incidence of depression, self-injury, and suicidal ideation based on the SMQ was balanced across the 2 treatment groups (10% IFN β-1a vs. 11% daclizumab). There was 1 completed suicide in the IFN β-1a group and none in the daclizumab group. The Beck Depression Inventory, Second Edition (BDI-II) showed no clinically meaningful changes from baseline over time and the Multiple Sclerosis Impact Scale 29-item (MSIS-29) Psychological Impact score showed greater improvement in the daclizumab group. Also relevant, co-medication used by MS patients did not differ between treatment groups regarding antidepressant, antipsychotic or anxiolytic agents.

There were no clinically significant changes in aggregate hematological laboratory values (i.e., white blood cell [WBC], lymphocyte, and neutrophil counts) for subjects who received daclizumab in the placebo-controlled and active-controlled experiences. The incidence of hematological AEs based on the hematopoietic cytopenia SMQ was comparable in the placebo-controlled and active-controlled

experiences (0% placebo vs. 2% Daclizumab 150 mg; 7% IFN β-1a vs. 8% Daclizumab 150 mg). There were no clinically meaningful differences in the incidence or type of hematopoietic cytopenias observed in daclizumab-treated subjects compared with placebo- or IFN β-1a-treated subjects. In the 5 out of 1785 daclizumab-treated subjects who experienced SAEs of hematological disorders or cytopenias, all had confounding factors, such as concurrent infections, concomitant medications that cause cytopenias, and other complications; or the events occurred after discontinuation of study treatment, suggesting that an association with daclizumab in these cases was unlikely. Overall, based on medical review of the available data, the limited number of events, and the presence of other contributory factors in most of the cases, there does not appear to be an increased risk of hematological cytopenias during treatment with daclizumab. Although there was no significant change in aggregate haematological laboratory values, the incidence of decreased post-baseline CD4+ (<400 cells/µL, <200 cells/µL) was 29% and 3%, respectively, and the incidence of decreased CD8+ counts (<200 cells/mm3, <100 cells/mm3) was 34% and 4%, respectively in the overall daclizumab group. However because of the risk of leucopoenia monitoring of White blood cells is recommended every 3 months. Also it should be mentioned that no information is available regarding the risk of PML following treatment with Zinbryta.

The incidence of malignancies was 1% in daclizumab-treated subjects and was balanced across the treatment groups. The rate of malignancy in daclizumab-treated subjects was comparable to the background rate of malignancy in the general population of patients with MS.

Based on positive and negative status for anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs), there did not appear to be any correlations with AEs and SAEs, including AESIs such as hepatic, cutaneous, infectious, hypersensitivity, and other potential immune-mediated events. These results suggest that immunogenicity did not have a discernible effect on the safety profile of daclizumab. Overall, based on the totality of the clinical study data, daclizumab has a positive benefit/risk profile that supports its use in a broad population of adult patients with relapsing forms of MS. In the clinical studies, statistically significant and clinically relevant beneficial effects were seen consistently on clinical, radiographic, and patient-reported outcome measures in subjects with MS. The safety profile has been well characterized, and specific guidelines to monitor and manage the risks have been implemented and tested in the trials. The most important risk of hepatic events and elevations of serum transaminases can be effectively managed through raising Investigator awareness of the risk and monitoring of serum transaminases to allow for early recognition of events and for initiation of actions that can be taken. Other important risks involving the skin, infections, depression and colitis have been manageable with standard medical care, such as antibiotics, corticosteroids, treatment discontinuation, as appropriate for the event. Based on the profiles of these events, their response to treatment, and the mechanism of action of daclizumab, the immunomodulatory effects of daclizumab treatment are implicated as a possible underlying factor and were important in the development of management guidelines for these events in consultation with clinical experts.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Transaminase elevations and serious hepatic injury Serious skin reactions Infections and serious infections Colitis Depression Serious lymphadenopathy
Important potential risks	Acute serious hypersensitivity reactions Opportunistic infections (including PML) Malignancies (particularly lymphoma) Sustained severe lymphopenia
Missing information	Use in patients under the age of 18 years Use in patients over the age of 55 years Use during pregnancy Exposure during lactation Use in patients with hepatic impairment Use in patients taking concomitant hepatotoxic medications

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Global paediatric study with 2 year treatment duration followed by 2-year extension (3)	To evaluate the activity, safety/tolerability, and PK of DAC HYP in patients from 10 to less than 18 years of age	Safety profile in patients under the age of 18 years	Planned	Submission date dependent on study dates. Study finish by August 2019 per the agreed PIP (EMEA-001349-PIP01-12-M01; Decision P/0147/2014)
Global Phase 4 pregnancy registry (109MS402) (3)	To prospectively evaluate pregnancy and infant outcomes in pregnant women with MS who were exposed to DAC HYP since the first day of their last menstrual period (LMP) prior to conception or at any time during pregnancy	Use during pregnancy	Planned	Planned final report: 2029
Epidemiological database study (3)	To assess the effectiveness of risk minimisation measures	Transaminase elevations/serious hepatic injury	Planned	Planned final report: Dependent on dates study is conducted
Central tracking of distribution of physician guide to HCPs in EEA (3)	To evaluate process indicators of effectiveness of the distribution of physician education materials	Transaminase elevations/serious hepatic injury	Planned	With PSURs
Feasibility study of MS registries (3)	To assess the feasibility of conducting PASS using MS registries	To assess whether important potential risks could be studied using MS registries	Planned	Report of feasibility assessment within 6 to 12 months of marketing in the EU

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Transaminase elevations and serious hepatic injury	Text in SmPC (4.4; 4.8) and Package Leaflet	Hepatic Risk Management Guide Patient Card
Serious skin reactions	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Infections and serious infections	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Colitis	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Depression	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Serious lymphadenopathy	Text in SmPC (4.8) and Package Leaflet	None
Acute serious hypersensitivity reactions	None [1]	None
Opportunistic infections (including PML)	Text in SmPC (4.4) and Package Leaflet [2]	None
Malignancy (particularly lymphoma)	None	None
Sustained severe lymphopenia	Text in SmPC (4.4) and Package Leaflet	None
Use in patients under the age of 18 years	Text in SmPC (4.2) and Package Leaflet	None
Use in patients over the age of 55 years	Text in SmPC (4.2) and Package Leaflet	None
Use during pregnancy	Text in SmPC (4.6) and Package Leaflet	None
Exposure during lactation	Text in SmPC (4.6) and Package Leaflet	None
Use in patients with hepatic impairment	Text in SmPC (4.2; 4.4) and Package Leaflet	None
Use in patients taking concomitant hepatotoxic medications	Text in SmPC (4.4) and Package Leaflet	None

[1] Acute serious hypersensitivity reactions have not been observed with DAC HYP but were observed with another form of the daclizumab antibody (Zenapax). Therefore, the prescriber and patient information include a contraindication for DAC HYP in patients with a history of severe hypersensitivity (e.g., anaphylaxis or anaphylactoid reactions) to daclizumab or to any of the excipients.

[2] An increased risk of opportunistic infection has not been observed with DAC HYP. SmPC and Package Leaflet provide information on infections and serious infections and a recommendation for tuberculosis screening and monitoring during treatment in patients who have had tuberculosis or who live in endemic areas of the disease.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zinbryta (daclizumab) is included in the additional monitoring list as a biological product that is not a new active substance but is authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.10. New active substance claim

2.10.1. Applicant's position

The applicant presented the following arguments to defend the claim of a new active substance:

Quality aspects:

The applicant claimed that daclizumab which is the active substance in Zinbryta, should be considered a new active substance as it significantly differs from the daclizumab in Zenapax with respect to the three key pillars for a biological active substance:

a. the host/vector (as the source material) used for expressing the recombinant glycoprotein, is different for Zinbryta;

b. the manufacturing processes, including the cell cultivation conditions and purification processes, are significantly different for Zinbryta; and

c. the resulting molecular structure is significantly and meaningfully different in terms of the glycosylation composition and structure of Zinbryta.

The main differences claimed relate to the use of a different expression system to generate a new recombinant cell line for Zinbryta, which was cultured under different conditions and without the use of animal-derived materials to produce a recombinant protein with a distinctly different glycosylation profile to Zenapax. A different sequence and set of purification steps was also used for Zinbryta, yielding a

product of high purity and demonstrating greater structural homogeneity than Zenapax. In particular, Zinbryta has lower levels of high mannose and other non-fucosylated glycans than Zenapax, and also lacks glycan structures of murine origin.

Non Clinical and Clinical aspects

The applicant claimed that structural glycosylation is a critical determinant of the therapeutic function of an antibody. In the case of Zinbryta, the differences in glycosylation (resulting from the modifications to the expression system and the cell cultivation conditions) manifest in significant differences in pharmacokinetic and pharmacodynamics properties which could change the safety and/or efficacy profile of the product and, therefore, differentiate daclizumab in Zinbryta from the daclizumab in Zenapax. These pharmacological effects seen with Zinbryta are related to:

a. differences in biological activity as measured by antibody-dependent cell-mediated cytotoxicity (ADCC)

b. in vivo clearance, and hence the extent of systemic exposure to the circulating therapeutic protein;

c. immunogenicity; and

d. binding to the biologically relevant receptors which are linked mechanistically to the homeostasis of T regulatory cells.

Differences in In Vitro ADCC Activity

Antibody-dependent cell-mediated cytotoxicity (ADCC) measures the killing of antibody-coated target cells by cytotoxic effector cells. This biological effect is triggered through interaction of target-bound antibodies with Fc gamma receptors (FcγRs) present on the surface of effector cells. IgG Fc glycans are required for optimal binding of the antibody to FcγRs and for the effector functions that control the clinical properties of some therapeutic antibodies [Arnold 2007; Shi and Goudar 2014]. Natural killer (NK) cells mediate ADCC. NK cells are activated to lyse target cells when Fc receptors expressed on the surface of NK cells binds the Fc portion of antibodies bound to target cells. CD16 (FcγRIII) is the predominant Fcγ receptor expressed on NK cells.

Consistent with the differences in glycan profile, Zinbryta had a significantly lower binding potency for CD16 than Zenapax as measured in an AlphaScreen competitive binding assay. The relative binding of Zenapax to CD16 is 156% compared to Zinbryta. As a result, Zinbryta induces less down-modulation of CD16 on NK cells than Zenapax under in vitro conditions designed to replicate those of the in vitro ADCC assay.

Consistent with the differences in CD16 binding and CD16 down-modulation on NK cells, Zinbryta has a significant reduction in ADCC activity in vitro when compared to Zenapax. The maximal ADCC activity achieved with Zinbryta tested at graded concentrations was approximately 30-40% lower than the activity elicited by the same concentration of Zenapax.

Zinbryta has significantly ($p<0.05$) reduced levels of in vitro cytotoxicity in comparison to levels observed for Zenapax when effects of increasing concentrations of antibody were evaluated against fixed Effector to Target (E:T) ratios. Antibody-dependent cytotoxicity was measured by 51Cr release from IL-2 receptor-expressing KIT-225 K6 target cells in the presence of human peripheral blood mononucleated (PBMC) effector cells. The level of cytotoxicity was calculated as a percentage of maximum cell lysis. Mean and Standard Error results were obtained from six independent experiments using peripheral blood mononuclear cells obtained from healthy donors.

Zinbryta has significantly ($p<0.05$) reduced levels of ADCC in comparison to levels observed for Zenapax when effects of a single antibody concentration was evaluated against changes in Effector to Target (E:T) ratios in vitro.

The differences in ADCC activity can be linked to the differences in glycan profile between Zinbryta and Zenapax. In particular, Zinbryta has lower levels of high mannose and other non-fucosylated glycans than Zenapax. High mannose (non-fucosylated) glycans are well described to enhance ADCC activity in vitro and target cell depletion in vivo [Shi and Goudar 2014]. This general effect of increased high-mannose glycans causing increased ADCC was specifically demonstrated for daclizumabFigure 13. A high-mannose daclizumab was generated and mixed with Zinbryta at varying percentages of antibodies with high mannose glycans to reflect varying glycan profiles. Reflecting the comparison between Zinbryta and Zenapax, as the percentage of high mannose species increases, ADCC activity increases. Thus, the glycan structural differences between Zinbryta and Zenapax are manifested as a change in biological activity, specifically as reduced in vitro ADCC activity for Zinbryta, which is relevant to an assessment of the safety profile.

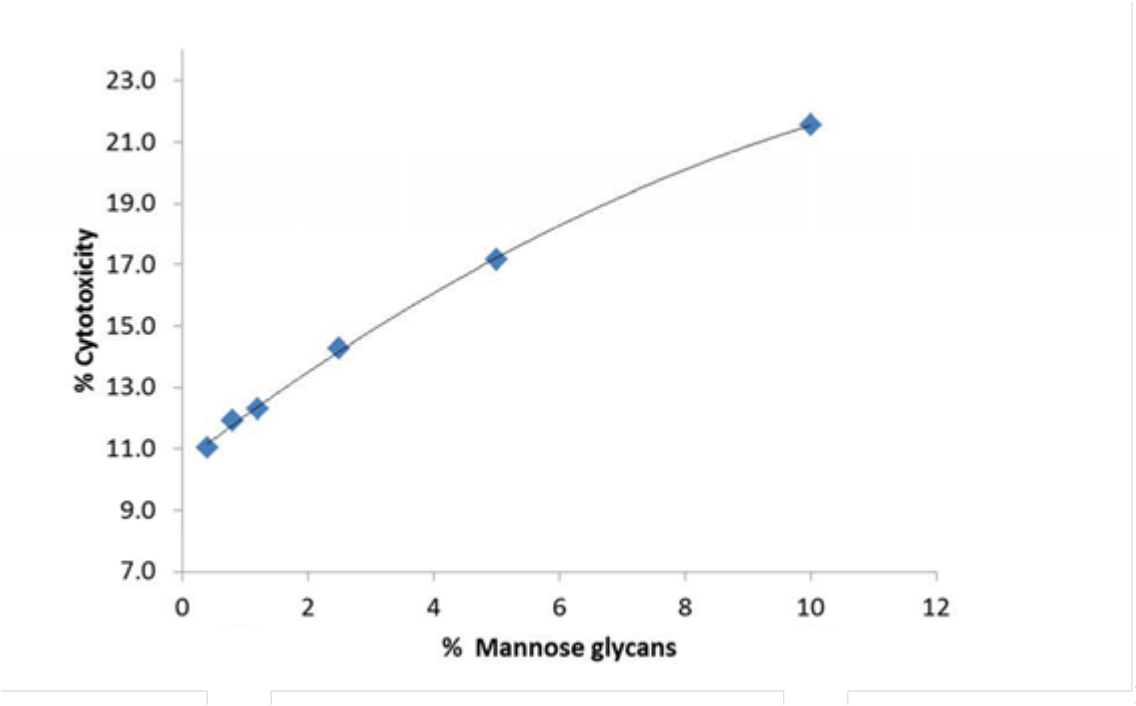


Figure 11: Correlation of High-Mannose Glycans with Daclizumab Cytotoxicity

Correlation has been demonstrated between the levels of mannose glycans in the sample and the percent in vitro cytotoxicity. High mannose afucosylated DAC (positive control with mannosylation of about 100%) was spiked into Zinbryta Drug Substance with initial 0.4% of mannose to produce samples with the following levels of mannosylation: 0.8, 1.2, 2.5, 5.0, and 10 %. In this study each sample was tested in duplicate at 3 different effector:target cell ratios with PBMCs from 3 different donors. Final % cytotoxicity represent averages for each sample across all replicates, effector: target cell ratios, and donors.

Differences in Clinical Immunogenicity as a Safety Measure

Glycan modifications of therapeutic antibodies directly impact functional properties and immunogenicity. Altered glycosylation patterns may decrease or increase the immunogenic properties of mAbs, e.g. alpha Gal. Non-typical glycosylation patterns, e.g. as encountered when adopting entirely novel expression systems, may introduce a higher immunogenicity risk as compared with more commonly used expression systems (Guideline on immunogenicity assessment of mAb intended for in vivo clinical use -

EMA/CHMP/BMWP/86289/2010). In this regard, the documented differences in glycosylation profile between Zinbryta and Zenapax are relevant.

Clinical data suggests a reduction in Zinbryta immunogenicity when compared to Zenapax. In the 205MS301 study, a large, Phase 3 trial of Zinbryta in MS patients, the persistent anti-drug antibody (ADA) and neutralizing antibody (NAb) responses were 7% and 2%, respectively. In comparison, the reported anti-idiotype immunogenicity of Zenapax is 14% (Zenapax US Prescribing Information, revised 2005)). Possible clinical consequences of higher immunogenicity include anaphylaxis, reduced drug half-life and neutralization of the therapeutic protein [van Beers and Bardor 2012]. Even though a direct comparison of the immunogenicity rates of the two products is not feasible, the observation of reduced Zinbryta immunogenicity is notable given that one would expect that Zinbryta would have higher immunogenicity than Zenapax, because the 205MS301 study was performed in immunocompetent MS patients, while the Zenapax trials were conducted in significantly immunosuppressed transplant patients. Furthermore, Zinbryta is administered by subcutaneous injection, which is considered a more immunogenic route of administration when compared to the intravenous route of administration used for Zenapax. In particular, it is well established that glycosylation can have an impact on antigenicity and immunogenicity [van Beers and Bardor 2012]. The structural differences in glycosylation between Zinbryta and Zenapax could account for the observed difference in immunogenicity profiles of the two products that could have a direct impact on safety and potency.

Differences in Clinical Pharmacokinetics

In addition to effects on ADCC, glycans can directly affect the pharmacokinetics of antibody therapeutics. In vivo studies in both humans and mice have shown that high mannose mAbs are cleared from serum more rapidly than mAbs of any other glycoform type [Goetze 2011; Kanda 2007; Shi and Goudar 2014]. Zinbryta, which contains a lower percentage of high mannose glycans as compared to Zenapax, has been reported to have an approximately 30% reduced systemic clearance as compared to Zenapax [Othman 2014]. This observation is consistent with a glycan-mediated clearance. [Alessandri, L et al 2012: Goetze, A.M., et al 2011].

Therefore, the structural differences between Zinbryta and Zenapax are also implicated in a change in human pharmacokinetics and hence systemic exposure to the therapeutic protein which is relevant to an assessment of the safety and efficacy profile of the product

Impact on Mechanism of Action

As regards the mechanism of action of Zinbryta in MS, the significant differences in ADCC between Zinbryta and Zenapax are directly linked mechanistically to the pharmacodynamic effects on regulatory T cells (Tregs) and to the assessment of the safety profile in MS patients.

Treg cells play a critical role in limiting immune activation and preventing autoimmune pathology [Sakaguchi 2008; Brusko 2008; Josefowicz 2012]. In preclinical and clinical studies, reductions in Treg numbers or reduction in Treg function are linked to the development of autoimmune pathology. Furthermore, there is increasing recognition of the importance of Tregs in limiting MS disease. Depletion of Tregs exacerbates animal models of MS and defects in Treg function have been reported in MS patients [Viglietta 2004; Kleinewietfeld and Hafler 2014; Costantino 2008]. Thus in the context of a therapy for MS, reductions in Tregs may increase incidence of autoimmune adverse events and potentially limit efficacy.

In vitro ADCC activity is taken as a relative indication of cell-killing capability in vivo. Tregs express very high levels of CD25, rendering them particularly susceptible to the cell killing by an ADCC promoting anti-CD25 specific antibody. The higher ADCC of Zenapax is considered an undesirable attribute as it

would potentially result in increased Treg depletion and increased incidence of autoimmune pathologies associated with therapy. In an animal model comparing two forms of an anti-CD25 antibody that differ only in Fc- mediated ADCC activity in vivo, the antibody with higher ADCC showed greater depletion of Treg cells (~50% vs. ~25% reduction in Tregs). Treatment with the highly-depleting antibody but not the antibody lacking ADCC activity, resulted in immune dysregulation and the emergence of a large proportion of pro-inflammatory lymphocytes.

Zinbryta therapy results in an approximately 50% reduction in circulating Tregs in MS patients [Huss 2014]. As best evidenced by the clinical benefit seen in MS, the aggregate impact of Zinbryta is a reduction in CNS autoimmune pathology [Gold 2013; Giovannoni 2014], but treatment with Zinbryta is also associated with risks of adverse immune-mediated events. A relationship between reductions in Tregs and the safety profile of Zinbryta is supported by the adverse event profile observed in Zinbryta treated MS patients which is consistent with a reduction in Treg mediated immune homeostasis. In both mice and humans genetic deficiencies in Tregs are characterized by inflammatory pathologies of the skin and intestinal tract, immune-mediated hepatitis, elevated IgE, lymphoproliferation, lymphoid hyperplasia and lymphadenopathy [Bezrodnik 2014; Goudy 2013; Caudy 2007; Sharfe 1997; Wildin 2002; Willerford 1995; Fontenot 2003]. An overlapping set of sequelae are observed in Zinbryta treated MS patients. Therefore, it can reasonably be hypothesized that further reductions in Tregs, driven by higher ADCC, may increase the incidence and/or severity of such events. In this context, the lower ADCC activity of Zinbryta compared to Zenapax is believed to be beneficial for safety by limiting the depletion of CD25-expressing Treg cells.

Based on these cumulative data, the applicant concluded that the change in glycan structure and corresponding reduction in ADCC assay observed in Zinbryta results in an antibody with a change in pharmacodynamic properties that may be relevant to an assessment of the safety profile.

2.10.2. Additional Applicant's justification provided in response to the request from the Committee

Further to the CHMP request for additional substantiation on the claim of new active substance for daclizumab in Zinbryta, the Applicant provided four specific areas of scientific justification, assumed to be relevant to differentiating the efficacy and safety profile of Zinbryta from Zenapax:

I. How post-translational modifications (and in particular differences in glycosylation) have likely affected immunogenicity and in vivo clearance of Zinbryta when compared to Zenapax.

II. Through PK-PD modelling, how the differences in clearance rates impact systemic drug exposure and dosing of the two products.

III. How the structural differences can impact ADCC and T regulatory (Treg) cell levels.

IV. How the depletion of Tregs can impact the safety profile. Data to show differences in cutaneous adverse events is provided in this regard.

I. Post-translational modifications and impact to clearance

Post-translational modifications (and in particular glycosylation) of a protein can affect its in vivo clearance. The Zinbryta N-linked glycosylation profile differs from that of Zenapax, and the distinct glycosylation profiles of these two products can be linked to the observed differences in clearance. Although the levels and types of glycans on the Fc domain do not impact binding to the FcRn receptor (Simmons et al., 2002; Ha et al., 2011), which gives antibodies their relatively long half-life compared to other therapeutic proteins, exposed glycans near the exterior of the antibody protein may impact clearance through other receptors. High mannose glycans in particular can directly affect the

pharmacokinetics of antibody therapeutics, whereas other glycan structures known to affect clearance of a range of glycoproteins (Solá and Griebenow, 2010) may have limited effect on antibody clearance.

Glycans can also affect immunogenicity. Differences in immune response can also impact the clearance and pharmacokinetics of the molecule. Clinical data suggests a reduction in the immunogenicity of Zinbryta when compared to Zenapax. In a large Phase 3 trial of Zinbryta in MS patients (Study 205MS301), the persistent anti-drug antibody (ADA) and neutralizing antibody (NAb) responses were 7% and 2%, respectively. In comparison, the reported anti-idiotype immunogenicity of Zenapax is 14% (Zenapax US Prescribing Information, revised 2005). Even though a direct comparison of the immunogenicity rates of the two products is not feasible, the observation of reduced Zinbryta immunogenicity is notable given that one would expect that Zinbryta would have higher immunogenicity than Zenapax, because the 205MS301 study was performed in immunocompetent MS patients, while the Zenapax trials were conducted in significantly immunosuppressed transplant patients. Furthermore, Zinbryta is administered by subcutaneous injection, which is considered a more immunogenic route of administration when compared to the intravenous route of administration used for Zenapax.

Possible clinical consequences of higher immunogenicity include anaphylaxis, reduced drug half-life and neutralization of the therapeutic protein (van Beers and Bardor, 2012). Population PK analyses showed that time-dependent NAb-positive status increased Zinbryta clearance by an average of 19%. Therefore, the structural differences between Zinbryta and Zenapax that are implicated in differences in immunogenicity can also lead to a change in PK and hence systemic exposure to the therapeutic protein. Differences in clearance between Zinbryta and Zenapax/DAC Penzberg have been observed in the clinic, based on Phase 3 data for Zinbryta as well as the DAC-1012 CHOICE study of DAC Penzberg. The totality of these clinical data further demonstrate non-similarity between Zenapax and Zinbryta and are supportive of the impact of glycosylation on both receptor-mediated clearance and immune antibody-mediated clearance, a finding that is consistent with what is available in the published literature for glycoproteins.

II. PK and dose-response analysis of Zinbryta vs. Zenapax/DAC Penzberg

In order to assess the impact that the above-noted changes in immunogenicity and PK have on clinical efficacy, the applicant has constructed population PK and dose-response models for Zinbryta and Zenapax using Gd-enhancing lesions on cranial MRI as the response variable. The use of this measure as a reflection of clinical outcome under treatment is appropriate as these lesions are believed to mediate clinical MS relapses and are empirically closely correlated with the relapse rate in this disease. The results of the PK and dose-response models demonstrate that MS patients treated with a monthly dose of Zenapax equal to the proposed clinical dose of Zinbryta would have meaningfully higher levels of brain inflammation as measured by Gd+ lesions on MRI. As such, these differences are reasonably predicted to translate directly into higher clinical MS relapse rates during Zenapax treatment as compared to Zinbryta treatment.

The most relevant data to perform this comparison of response come from the SELECT study (205MS201) with Zinbryta and the CHOICE study (DAC-1012) with DAC Penzberg, a form of daclizumab that is structurally identical to Zenapax. Both studies were conducted in populations of MS patients with similar demographics and baseline characteristics (Table 33). In both studies the mean EDSS, age and baseline Gd lesions were similar. There was a slightly higher proportion of subjects who were female in CHOICE (74.3% versus 65% in SELECT). The history of relapse at baseline was similar after accounting for the difference in the time interval history. As outlined above the data from these studies were used to establish the dose-response relationship and model the efficacy impact of the lower exposures expected with equimolar doses of Zenapax/DAC Penzberg vs. Zinbryta.

Table 33: Summary of demographics and baseline disease characteristics

	SELECT (205MS201)			CHOICE (DAC-1012)		
	Placebo (n=204)	DAC HYP 150 mg (n=208)	DAC HYP 300 mg (n=209)	Placebo (n=77)	1 mg/kg (n=78)	2 mg/kg (n=75)
Age (years)	36.6 (9.0)	35.3 (8.9)	35.2 (8.7)	40.8 (9.0)	38.2 (9.3)	40.4(8.5)
Female: n %	128 (63)	140 (67)	134 (64)	55 (71.4)	58 (74.4)	58 (77.3)
Weight (kg)	70.0 (14.4)	68.3 (15.9)	68.2 (15.2)	77.5 (18.0)	73.6 (16.8)	80.7 (19.9)
Number of Gd lesions	2.0 (4.5)	2.1 (3.5)	1.4 (3.3)	1.1(2.7)	2.7 (7.0)	0.8 (1.7)
Relapses past year	1.3 (0.6)	1.4 (0.7)	1.3 (0.7)	na	na	na
Relapses past two year	na	na	na	2.6 (1.7)	2.6 (1.6)	2.4 (1.2)
Baseline EDSS	2.7 (1.2)	2.8 (1.2)	2.7 (1.2)	3.0 (1.2)	3.0 (1.2)	3.0 (1.3)

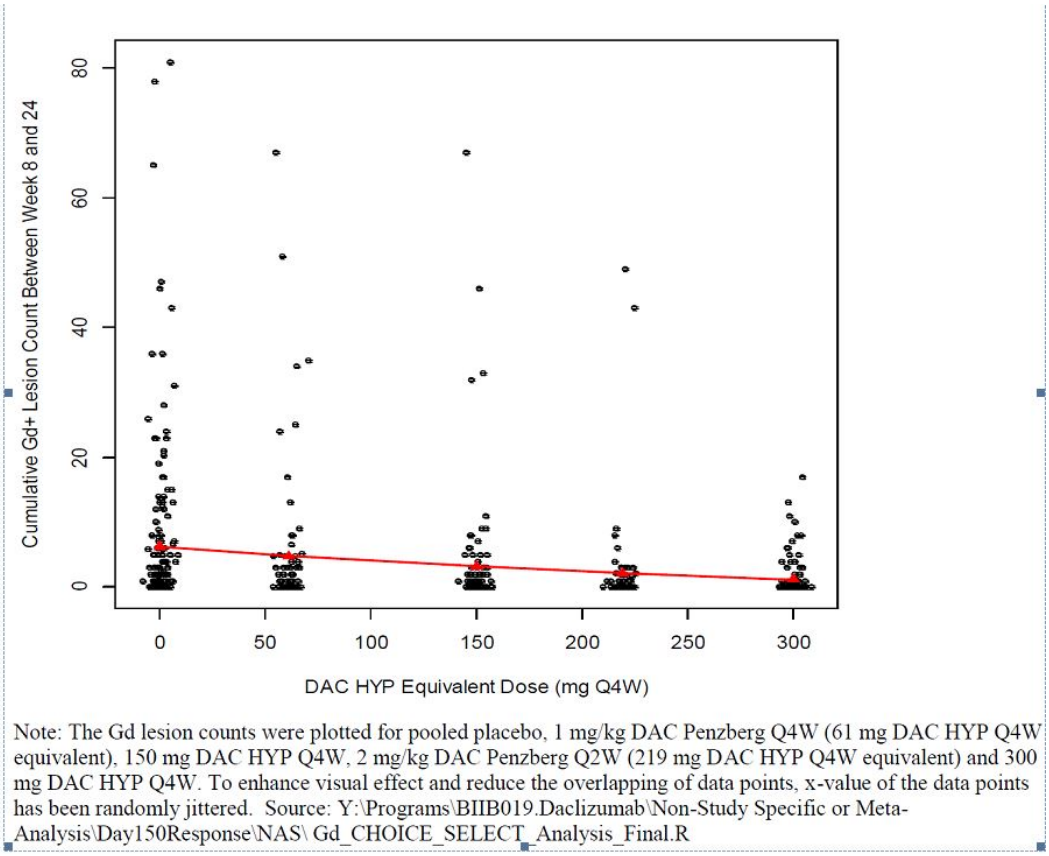
Note: Numbers presented are mean and standard deviation unless otherwise noted. na = Not available

In summary, the combined PK and dose-response models estimate a 27% increase in the mean number of new Gd+ lesions between Week 8 and Week 24 using 150 mg Q4 Weeks of DAC Penzberg as compared to 150 mg Q4 weeks of Zinbryta. There is strong association between the effect of treatment on MRI lesions and the effect on relapses, and, based on prior quantitative analyses of the relationship between these two variables for MS immunomodulatory therapies, this increase in Gd lesions is expected to result in approximately a 13% increase in relapse rate in 150 mg Q4W of DAC Penzberg compared to 150 mg Q4W of Zinbryta (Sormani and Bruzzi, 2013).

Applicant's conclusions from population PK and dose-response modelling

The simulated PK (steady-state AUC) of the two products derived using Population PK models of clearance for each product resulted in a finding that 150 mg of DAC Penzberg is estimated to be approximately equivalent to 110 mg Zinbryta with regard to resulting systemic exposure. Based on the simulated steady-state AUC differences, the body weight-based dose regimens evaluated in the CHOICE study using DAC Penzberg were converted into equivalent Zinbryta Q4W dose levels, and a dose-response model was fitted to the cumulative new or enlarging Gd lesion count between Week 8 and Week 24 in CHOICE and SELECT. The analysis suggested a significant dose-response relationship for the cumulative Gd lesions described using a negative binomial model (Figure 14). The point estimate (95% CI) for the dose effect is -0.0059 (-0.0073, -0.0045), with a corresponding p-value <0.0001.

From the estimated dose-response relationship, the mean Gd lesion count was estimated for doses of 150 mg Zinbryta Q4W and 110 mg Zinbryta Q4W (determined to be equivalent to 150 mg Q4W of DAC Penzberg, as described above). Assuming a population with an average baseline Gd lesion count of 1.77, it is estimated that the mean (95% CI) new Gd lesion count between Week 8 and Week 24 would be 2.16 (1.82, 2.51) for 150 mg Zinbryta Q4W and 2.74 (2.31, 3.19) for the 150 mg DAC Penzberg Q4W dosing. This equals a 27% approximate increase in the mean number of new Gd+ lesions between Week 8 and Week 24 of therapy for 150 mg DAC Penzberg Q4W compared to 150 mg Zinbryta Q4W, and a 13% increase in the annual relapse rate (ARR). Since a key goal of using daclizumab in MS patients is to reduce brain inflammation and clinical relapses, this distinct difference in the expected relapse rate and number of new Gd+ lesions during treatment with DAC Penzberg vs. Zinbryta should be clinically meaningful.



Note: The Gd lesion counts were plotted for pooled placebo, 1 mg/kg DAC Penzberg Q4W (61 mg DAC HYP Q4W equivalent), 150 mg DAC HYP Q4W, 2 mg/kg DAC Penzberg Q2W (219 mg DAC HYP Q4W equivalent) and 300 mg DAC HYP Q4W. To enhance visual effect and reduce the overlapping of data points, x-value of the data points has been randomly jittered. Source: Y:\Programs\BIIB019.Daclizumab\Non-Study Specific or Meta-Analysis\Day150Response\NAS\ Gd_CHOICE_SELECT_Analysis_Final.R

Figure 12: Observed cumulative new or enlarging Gd lesion count between Week 8 and Week 24 vs. Zinbryta equivalent dose every 4 weeks.

Table 34: Percentiles of stimulated steady state AUC for 150 mg Q4W based on Population PK model

Dose (mg Q4W)	Steady State AUC (ug/mL*hr)	DAC HYP	Penzberg	Ratio (DAC HYP/Penzberg)
150	5%	8486	6276	
	25%	12204	8995	
	50%	15445	11311	1.37
	75%	19299	14548	
	95%	25520	20400	

Source: Y:\Programs\BIIB019.Daclizumab\Non-Study Specific or Meta-Analysis\Day150Response\PKSim\SimData_Gen.R; Y:\Programs\BIIB019.Daclizumab\Non-Study Specific or Meta-Analysis\Day150Response\PKSim\SimData_Analysis.R

III. Impact of Structural Differences on Biological Function and T Regulatory Cells

Glycosylation of therapeutic antibodies can affect their functional properties, with an impact on Antibody-dependent Cell-Mediated Cytotoxicity (ADCC) being widely reported (Thomann et al, 2015). The Zinbryta N-linked glycosylation profile is distinct to that of Zenapax, and these differences have been linked to differences in ADCC between the two products that are linked mechanistically to pharmacodynamic effects on regulatory T cells (Tregs). In vitro ADCC activity is taken as a relative indication of cell-killing capability in vivo. Tregs express very high levels of CD25, rendering them particularly susceptible to the cell killing by an ADCC-promoting anti-CD25 specific antibody. The higher ADCC of Zenapax is considered an undesirable attribute as it increases the risk of Treg depletion and an increased incidence of autoimmune pathologies associated with therapy.

IV. Relevance of Treg cell suppression for safety and cutaneous adverse events

Clinical relevance of Treg suppression

A key clinical consequence of Treg suppression during daclizumab use in MS is believed to be a higher incidence of cutaneous adverse events, as a similar pattern of cutaneous adverse events is observed in conditions of known Treg cell deficiency. During clinical use of daclizumab, the risks of Treg suppression are partly balanced by the effects of CD25 antagonism on the effector T-cell response as well as the expansion of immunoregulatory CD56bright NK cells. When daclizumab treatment is stopped, the process of antibody elimination and reversal of the immunoregulatory effects that are caused by anti-CD25 treatment create a dynamic period in which the risks associated with Treg antagonism could theoretically be increased in some patients, particularly if Treg suppression is substantial and has not recovered by the time the other immunoregulatory effects of daclizumab have reversed.

Evidence for the involvement of Tregs

- In the CHOICE study with DAC Penzberg, there was evidence of an increased incidence of cutaneous adverse events during the washout period as compared to the on-treatment period. For example, during the 6-month washout period with DAC Penzberg, the incidence of the most common cutaneous AE “rash” was 8.1 % compared to an incidence of 3.3% during the 6-month on-treatment period (Study DAC1012 CSR).
- In contrast the increased risk of a cutaneous adverse event during the washout period was not observed with Zinbryta use when assessed using a randomized withdrawal design in study 205MS202. During Zinbryta washout, the incidence of “rash” during the 6-month washout period was 2% (Study 202) as compared to 2% during the initial 6-month on-treatment period.

Therefore, given the higher level of ADCC and greater antagonism of Tregs expected with Zenapax treatment, as well as the clinical data indicating differences in the safety profile, MS patients treated with

Zenapax may be at increased risk of cutaneous adverse events during the treatment washout period as compared to treatment with Zinbryta.

OVERALL CONCLUDING ARGUMENTS BY THE APPLICANT:

Overall, the Applicant was of the view that the findings presented support that there is a clinically significant impact of the structural differences in the glycan profile and resulting changes in PK, immunogenicity, and ADCC between DAC Penzberg/Zenapax vs. Zinbryta.

1. First, these differences result in a lower exposure with use of Zenapax/DAC Penzberg as compared to Zinbryta that would expose MS patients to meaningfully higher risks of brain inflammation and clinical relapses (estimated 27% increase in new Gd+ lesions over 16 weeks of treatment and an anticipated 13% increase in ARR in subjects treated with Zenapax vs. Zinbryta). Since a key goal of using daclizumab in MS patients is to reduce brain inflammation and clinical relapses, this distinct difference in the expected relapse rate and number of new Gd+ lesions during treatment with DAC Penzberg vs. Zinbryta should be clinically meaningful.
2. Second, while the effects of Treg antagonism may be partially balanced by other immunomodulatory effects of CD25 blockade during the on-treatment period, patients with greater Treg suppression may be at higher risk during the washout period. The clinical data obtained during washout with DAC Penzberg vs. Zinbryta support that the known structural differences between DAC Penzberg /Zenapax vs. Zinbryta translate into significant differences in the clinical safety profile of daclizumab in the target MS population.

The totality of the data available indicate that the structural distinctions in glycosylation between Zenapax and Zinbryta result in differences in PK and immunogenicity which directly impact the risk-benefit of daclizumab use in MS, and support the designation of Zinbryta as a new active substance. The magnitude and significance of these differences would preclude an assumption of biosimilarity, should these be presented in the context of a biosimilar application. As the two products could not be considered comparable from a therapeutic perspective, a full clinical development program was necessary to confirm the safety and efficacy of Zinbryta in MS, and accordingly an application for marketing authorisation was submitted under Article 8.3 of the Directive.

2.10.3. CHMP Scientific evaluation of the Applicant's position

Assessment of the Applicant's arguments on the quality aspects

The applicant claims that Zinbryta was developed starting from a distinct proprietary expression vector, NS0 sub-strain host cell line, and a new manufacturing process, that results in a new active substance different from the one previously authorised in the EU (i.e. daclizumab contained in Zenapax).

a) the host/vector (as the source material) used for expressing the recombinant glycoprotein, is different for Zinbryta

The Applicant indicates that a different expression vector was used in a different recombinant cell line. The MCB for Zinbryta is said to be generated using a different recombinant cell line to Zenapax, although it was derived from a substrain of the old recombinant NS0 cells by a series of subcloning, expanded and frozen as seed bank. The present MCB was generated from this seed bank expanded in serum-free medium. The gene expression generates the same amino acid sequence of Zinbryta and Zenapax albeit with minor differences in the Heavy Chain N-terminus, either from unprocessed signal sequence or with changes frequent in this type of products. Differences solely in the regulatory components of the

expression system of the same genetic sequence leading to the same amino acid sequence are not considered valid for the establishment of NAS.

b) the manufacturing processes, including the cell cultivation conditions and purification processes, are significantly different for Zinbryta; and

Again, the present considerations on differences in manufacturing process cannot be considered sufficient *per se* to qualify the active substance as NAS. It is recognised that different culture conditions might impact on molecular features of the molecule that might be of relevance for the pharmacological action or pharmacodynamics. Nevertheless, from a quality point of view, changes in the process such as growth medium, additional polishing step as well as a different manufacturing facility or different manufacturer cannot be the basis to confer the NAS status as they in itself do not lead to significant quality changes that could translate in significant differences in S/E.

c) the resulting molecular structure is significantly and meaningfully different in terms of the glycosylation composition and structure of daclizumab in Zinbryta.

The Applicant reiterates that Zinbryta glycosylation profile differs from Zenapax both in terms of glycan distribution and the types of oligosaccharides formed. The majority of the N-linked glycans on Zinbryta display very little heterogeneity, while the glycan profile for Zenapax is much more heterogeneous. The predominant glycan species are asialylated core-fucosylated bi-antennary structures. There is a lower abundance of high mannose forms and other non-fucosylated forms compared to Zenapax.

It is agreed that core fucosylation is important in modulating the affinity of the Mab to the Fc gamma receptor binding present in effector cells with implication in ADCC. Nevertheless, from the data provided, it is questionable to consider as major the differences in the relative percentages of the total amount when all fucosylated forms are added.

The other difference claimed is on the different proportion of uncapped mannose forms. The Applicant presented data on ADCC increase according to the relative content of mannose. Again, the significance of such differences are difficult to establish solely in terms of *in vitro* studies as various factors contribute both synergistically as well as antagonistically to the affinity to the Fc gamma receptor and ADCC and the behaviour *in vivo*. Also *in vivo* clearance of the exposed mannose forms through the Man-6-P receptor in lysosomes should be considered.

Structural glycans may have an impact in the various studies *in vitro* based upon antibody Fc domain interactions with Fc receptors (FcRs) expressed on lymphocytes. Nevertheless, ADCC was not considered to be the primary mode of action for this product targeted to compete with the IL-2 receptor present in activated lymphocytes. This CD25 binding was the mechanism of action considered for potency determination measuring proliferation inhibition of T-cell expressing CD25 when exposed to IL-2. CD25 binding is not affected by variations in the content of these various glycan variants.

CHMP Conclusions on the quality aspects:

From a quality point of view, the differences identified cannot be considered significant. In particular:

a) the differences in the expression system do not result in differences in the amino acid sequence,

b) the differences in the manufacturing process such as different growth medium and an additional polishing step do not lead to differences in the amino acid sequence.

c) Structural differences observed were related to differences in glycan profile that are known to impact Fc mediated ADCC and reflect a more homogeneous preparation. Variability of glycosylation is a known condition and co-existence of variants with differences in glycosylation does not imply to have a major

impact in vivo. Glycosylation is generally not considered a distinctive attribute unless the primary mode of action is associated to a specific structure and a given function related to the indication.

ADCC was not considered to be the primary mode of action for this product targeted to compete with the IL-2 receptor present in activated lymphocytes. This CD25 binding was the mechanism of action considered for potency determination measuring proliferation inhibition of T-cell expressing CD25 when exposed to IL-2. CD25 binding is not affected by variations in the content of these various glycan variants.

In order to further substantiate the NAS claim, it is required to establish whether the differences in glycosylation profile translate in significant differences in terms of safety and/or efficacy. This can only be addressed more appropriately at the non-clinical and clinical level.

CHMP assessment of the Applicant's arguments on the non-clinical aspects:

The applicant has presented in vitro data showing that the material differences in glycosylation (resulting from the modifications to the expression system and the cell cultivation conditions) manifest in significant differences in:

- differences in biological activity as measured by antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro;

- in vivo clearance, and hence the extent of systemic exposure to the circulating therapeutic protein;

- immunogenicity ;

- binding to the biologically relevant receptors which are linked mechanistically to the homeostasis of T regulatory cells.

Although a direct clinical comparison of the immunogenicity and pharmacokinetic rates of the two products was not feasible, non-clinical data were provided by the applicant to demonstrate differences in ADCC activity, immunogenicity, pharmacokinetics and pharmacodynamics.

CHMP Conclusions on non-clinical aspects:

From a non-clinical perspective data were provided to reveal differences in ADCC activity, immunogenicity, pharmacokinetics and pharmacodynamics that may be relevant to assume a different safety and efficacy profile of Zinbryta, but these needed to be further confirmed by clinical data.

Taking into account the clinical assessment and the clarifications provided by the company during the assessment, it became clear that the assumptions arising from the non-clinical data did not translate into a clinically relevant safety and efficacy different profile for Zinbryta when compared to Zenapax, as further elaborated below.

CHMP assessment of the Applicant's arguments on the clinical aspects:

Differences in glycan profile and ADCC activity have been elaborated further during the procedure. The argument centres on the differences in ADCC observed and the mechanistic link to the pharmacodynamic effects on regulatory T cells (Tregs) and to the assessment of the safety profile in MS patients. The role of Treg cells in limiting immune activation and autoimmune pathology is discussed in the context of the pathophysiology of MS. Reduction in Treg cells are hypothesised to increase incidence of autoimmune events and potentially limit efficacy. The Applicant provided details supporting this hypothesis. The higher degree of ADCC in Zenapax is considered by the applicant to potentially increase Treg depletion relative to Zinbryta with the associated consequences concerning safety and efficacy from increased autoimmune pathologies. This leads the Company to conclude that the lower ADCC activity of Zinbryta compared to Zenapax is potentially beneficial for safety by limiting the depletion of CD25-expressing Treg cells.

From the data available on MS patients treated with daclizumab manufactured at Penzberg (DAC Penzberg), the safety data – namely regarding Nabs against daclizumab, favours Zinbryta over DAC Penzberg with 7.9% NAbs in MS patients treated with doses up to 200 mg in study DAC 1012) against the frequency of 2% of Nabs with Zinbryta. The NAbs of Zenapax in a different population is less prone to an adequate comparison. The Applicant claims that this is indicative of Zenapax being potentially more immunogenic than Zinbryta in the absence of direct comparison of immunogenicity via a head to head clinical study. This information is unexpected given the relative immunogenicity of the different routes of injection (intravenous for Zenapax and subcutaneous for Zinbryta).

Glycan mediated clearance has been discussed and reference made to published data which reports Zinbryta has a 30% reduced clearance rate compared to Zenapax.

There are no clinical data adequately comparing efficacy of Zenapax and Zinbryta in MS patients.

The applicant argued that, based on the immunological responses observed for DAC Penzberg, Zenapax and Zinbryta, which may correlate to the differences in the glycan profile, there should be a significant difference in clinical properties. A significant part of the claim of the clinical significance of the differences in the quality profiles between Zenapax and Zinbryta was hypothesised by extrapolation of available clinical information and based on biological and clinical plausibility. The CHMP considered though that the applicant's argumentation and data provided were insufficient to substantiate that the differences observed with Zinbryta translate into significant differences in term of safety and efficacy.

The Applicant followed to present in further detail the differences in molecular structure and how this would impact upon clinical response, namely: a) PK modelling comparing clearance and extrapolating the impact on efficacy; b) how these differences could be clinically meaningful; c) how Zinbryta lower Treg depletion could translate into potential beneficial safety outcomes; and d) describe the observed differences in immunogenicity.

Regarding the PK/PD impact of glycosylation and the potential meaning of these differences, the presented model exhibited several problems:

- the applicant used a 90% confidence interval instead of the usual 95% to show non-equivalence;
- the applicant assumed that patients weighed a mean of 75 kg (DAC-1012 dosing being 1mg/kg Q4W – max dosing 100 mg or 2 mg/kg Q2W – max dosing 200 mg per visit 6 doses max) while in trial 205MS201 dosing was 150 or 300 mg Q4W 6 month treatment.
- Moreover, all DAC1012 patients were on beta interferon (IfN) treatment while all 205MS201 were not.

Considering all these aspects, the clinical data provided could not be considered comparable, as the population was substantially different, and the administered treatment was also not identical. Likewise, the prediction of 14% lower exposure of DAC Penzberg as compared to Zinbryta could not be directly linked to an improved efficacy profile, as the DAC Penzberg was tested in patients receiving beta IfN treatment.

The applicant tried to highlight that patients on DAC Penzberg had 12.6% more cutaneous AEs as compared to placebo whilst patients on Zinbryta had only 7% more cutaneous AEs as compared to placebo. Again, the CHMP considered that in this case the population was different: in the placebo arm, 26% of DAC 1012 patients exhibited cutaneous events while in the 205MS201 placebo arm only 13% had cutaneous AEs. Moreover, cutaneous AEs were more frequent in the DAC 1012 trial than in the 205MS201.This fact (which reduces the clinical relevance of these AEs for effectiveness and safety), and more importantly the fact that the DAC 1012 population was concomitantly treated with beta IfN further

supports the conclusion that the data provided cannot be considered sufficient to demonstrate a clinically significant benefit in either efficacy or safety.

CHMP conclusions on clinical aspects

The Applicant provided arguments to justify that daclizumab from Zenapax and daclizumab from Zinbryta should be considered different active substances. The Committee's conclusions, addressing in detail the different sections of the argumentation are as follows:

I. Post translational differences have been noted, however the amino acid sequence of daclizumab in Zinbryta is unchanged from the daclizumab in Zenapax. The pharmacodynamic properties of Zenapax are not seen to be very different from those of Zinbryta as demonstrated by a similar text in section 5.1 of the SmPC for Zenapax (now withdrawn), compared to that proposed for Zinbryta.

II. Differences in clearance were noted but the use of different PK models for Zinbryta and DAC Penzberg was not considered acceptable. The Applicant subsequently presented a new PK model, where all data were included and the effect of the different agents on clearance was evaluated. The relevance of this effect was noted by presenting a 90% CI based on 1000 bootstraps with values of 1.13 (1.02 – 1.26) for the ratio between DAC Penzberg and Zinbryta typical clearance. The Applicant claimed that this showed lack of bioequivalence between the two active substances. However, the bootstrap procedure is used to evaluate the relevance of the estimation of a particulate parameter, and in this case, typically a 95% CI would be calculated. Although this 95% CI was not presented, it is possible that the lower bound will be below 1 and the difference in clearance would not be statistically significant. As a consequence, the data from the new model cannot support the Applicant's claim that Zinbryta has lower in vivo clearance than DAC Penzberg.

III and IV. The structural differences are noted and could result in different ADCC activity, however the clinical impact of this cannot be measured but only hypothesised.

The applicant notes that in the CHOICE study (DAC 1012) with DAC Penzberg, there was an increased incidence of cutaneous adverse events during the washout period as compared to the on-treatment period, with an incidence of the most common cutaneous AE "rash" was 8.1 % in the wash-out period compared to an incidence of 3.3% during the 6-month on-treatment period. This actually relates to 5/123 patients during treatment and in 12/153 in the washout period. There is no discussion in terms of severity of the rash or whether this resulted in a discontinuation of treatment in the treatment period.

In study 205MS201/2 the incidence of "rash" during the 6-month washout period was 2% as compared to 2% during the initial 6-month on-treatment period; however the incidence of "rash" in the placebo group on treatment is very different to that seen in study DAC 1012 (1% 205MS201 vs. 5.2% DAC1012) making it difficult to conclude on the differences in safety profile.

It has been previously advocated that higher rate of immunogenicity was seen with Zenapax/DAC Penzberg (~8% NAbs vs. 2% with Zinbryta) and that NAbs cause an additional increase in antibody clearance. However this cannot be considered on its own to be significant and sufficient difference in safety or efficacy to justify a NAS status.

Of note, study DAC 1012 differed from study 205MS201/2 in several aspects:

a) study population: in DAC 1012 all patients were treated withIFN-beta and DAC Penzberg or placebo, whilst in 205M201/2 DAC was given as monotherapy;

b) dosing: for DAC1012 max dose was 100 mg per dosing visit in the 1mg/kg Q4w arm, and 200 mg per dosing visit in the 2mg/kg Q2w (IV over 15 minutes) vs 150 mg or 300 mg per dosing (subcutaneous), Q4w;

c) development phase: in the earlier phases, investigators and patients are more attentive to adverse events, and may report better and more adverse events; and

d) treatment duration.

Both clinical observation data – primary and secondary endpoints - and MRI lesion data are insufficient to allow for a decision on whether there is a difference between products based on clinical grounds.

As a conclusion, the discussion of the available data does not provide sufficient evidence of a difference in terms of clinical response (efficacy or safety) to support the relevance of the claimed structural differences between Zinbryta and Zenapax and, consequently, to support the NAS claim through demonstration of significant differences in terms of safety and/or efficacy.

CHMP OVERALL CONCLUSIONS ON THE NEW ACTIVE SUBSTANCE CLAIM:

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP decided that there are insufficient data to demonstrate that the observed differences for Zinbryta would translate into significant differences in terms of safety / efficacy compared to the previously authorized product that could support the NAS claim. Based on the overall assessment it is concluded that Daclizumab in Zinbryta cannot be qualified as a new active substance.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of daclizumab has been tested in 2 randomized, double-blind, controlled, pivotal studies. In 1 study (Study 201), the efficacy of daclizumab was compared to placebo, and in the other study (Study 301), the efficacy of daclizumab was compared to a current standard of MS treatment, IFN β-1a. Both of these studies demonstrated consistent treatment effects of daclizumab across validated clinical, radiographic, and patient-reported MS outcome measures. The effects of DAC HYP were apparent after the first dose as defined radiographically and within 3 months as defined by clinical endpoints. The benefits of daclizumab were then sustained over up to 3 years during continuous treatment.

Both clinical studies enrolled a broad population of RRMS patients who had had relapses. The mean age of subjects was approximately 36 years, and the percentage of subjects with highly active MS (≥ 2 relapses in the prior year and ≥ 1 Gd+ lesion on baseline MRI) at study entry was 16% - 21%. In both studies, a minority of enrolled subjects had received prior DMT, but the proportion was higher in Study 301 (41%) compared to Study 201 (20%).

The primary endpoint of both Studies 201 and 301 was the annualized relapse rate. Both studies demonstrated a robust effect of daclizumab on the reduction in clinical MS relapses: a 54% reduction versus placebo in Study 201 and a 45% reduction versus IFN β-1a in Study 301. Relapse rate in the daclizumab-treated subjects was 0.211 over 1 year in Study 201 and 0.249 over 1 year in Study 301. The annualized relapse rate for severe or serious relapses in the daclizumab arm at 1 year was 0.096 in Study 201 and 0.094 in Study 301.

Daclizumab treatment resulted in a 70% reduction in new or newly enlarging T2 lesions compared to placebo at 1 year in Study 201 and a 54% reduction compared to IFN β-1a at 2 years in Study 301 ($p < 0.0001$ for both comparisons). Gd enhancement, T2 lesion volume and the number and volume of T1

hypointense black holes also have shown a consistent and robust effect of daclizumab by Week 24 and sustained for the duration of daclizumab treatment.

In both pivotal studies, there was some evidence that daclizumab reduced the risk of confirmed disability progression. In Study 201, daclizumab reduced the risk of 12-week confirmed disability progression by 57% relative to placebo (p = 0.0211) and the risk of 24-week confirmed disability progression by 76% (p = 0.0037). In Study 301, daclizumab reduced the risk of 12-week confirmed disability progression by 16% (p = 0.1575) [not statistically significant] and the risk of 24-week confirmed disability progression by 27% (p = 0.0332). The differences in the daclizumab efficacy estimates for disability progression between Studies 201 and 301 are consistent with the established effect of IFN β-1a on confirmed disability progression compared to placebo (37% vs. placebo in registrational studies). Overall, the magnitude of the treatment effect on confirmed disability progression against IFN β-1a in Study 301 (16% to 27% reduction) is confirmatory of the 57% to 76% reduction in confirmed disability progression against placebo in Study 201, recognizing the effect of IFN β-1a on this endpoint.

In Study 301, confirmed disability progression was common after a tentative disability progression among subjects with at least one tentative disability progression in the trial: 35% for 12-week confirmed progression and 24% for the 24-week confirmed progression. Censoring after a tentative disability progression was nearly twice as common in the IFN β-1a group compared to the daclizumab group (43 vs. 24 for the 12-week confirmed progression), reflecting a proportionally higher number of tentative disability progressions in the IFN β-1a arm of the trial. While the number of subjects censored after a tentative disability progression (n = 67) was small relative to the total number of subjects with a tentative disability progression in the trial (n = 736), assumptions made about disability progression in these censored subjects impacted whether the test of statistical significance for disability progression was above or below the 0.05 significance threshold in Study 301. Prespecified analyses of disability progression in Study 301 supported a significant treatment effect of daclizumab over IFN β-1a on both 12- and 24-week confirmed disability progression analyses, except when analysed under the assumption that disability progression did not occur in any patient who was censored after a tentative disability progression.

Additionally, a positive effect on disability progression in all forms of RMS, including the relapsing forms of Secondary Progressive Multiple Sclerosis was demonstrated. In the clinical development of daclizumab in MS, the 2 pivotal trials were of sufficient duration and size that certain subjects included in these trials could during the trials be identified as having SPMS with superimposed relapses based on the observation of sustained disability progression that occurred independently of, or in the absence of, clinical relapses. Furthermore, analysis of these subjects provided evidence that daclizumab was more effective than IFN β-1a at preventing the progression of sustained disability progression that occurred independently of clinical relapses. This finding, in conjunction with the analyses provided, demonstrating efficacy of daclizumab in subjects with both highly active (approximately 40% of subjects) and less active (approximately 60% of subjects) forms of MS, demonstrated that daclizumab has efficacy across a broad spectrum of MS subjects which was considered essential in an indication for “relapsing forms of MS.”

Uncertainty in the knowledge about the beneficial effects.

The extrapolation of annualised relapse rate to more than the study period adds significant uncertainty: it is not known for the individual patient, when they are going to progress to SPMS, particularly when limited number of patients with high disease activity were included in the clinical studies. The assumption of whether daclizumab has any efficacy over non-RMS (efficacy on secondary progressive MS) was discussed, but there is still uncertainty on the magnitude and duration of such an effect.

The number of new lesions per time unit is a known relevant endpoint, but in the individual patient, the locations of the new lesions are very important, depending whether they occur in more loquacious or silent areas of white matter.

Disability was measured by the use of EDSS and it has to be taken into account that EDSS is not a disability tool, as interpreted like the disruption of the patient in his role within society, but is more an impairment tool. Nevertheless, there seems to be a reasonable correlation between impairment as measured by EDSS and disability.

Risks

Unfavourable effects

The safety of Daclizumab 150 mg has been well characterized in clinical studies of 1785 MS subjects treated for up to 6 years, accounting for approximately 4100 subject-years of exposure. During the accumulation of these safety data, several important risks have emerged, including elevations of liver transaminases and hepatic injury, cutaneous events, infections, and depression and strategies and approaches to monitor and mitigate these risks have been implemented and tested in the clinical studies.

Daclizumab is associated with a risk of elevations of serum transaminases and cases of hepatic injury. Most often this risk manifests as a transient and asymptomatic increase in ALT/AST that resolves spontaneously or with discontinuation of dosing. In a small number of cases, serious events of hepatic injury, characterized by concomitant elevations of serum transaminases and bilirubin, were identified in which daclizumab may have played at least a significant contributory role based on independent adjudication of the events. With the exception of a fatal case of autoimmune hepatitis early in the clinical development program, prompt identification of these cases, discontinuation of daclizumab, and treatment of underlying or other contributory causes resulted in favourable outcomes. While a single dose of daclizumab given at the time of a transaminase abnormality generally did not appear to worsen or prolong events, the single case of fatal autoimmune hepatitis occurred in the setting of repeated administration of daclizumab during the elevation. Treatment discontinuation for patients meeting certain criteria (and possibly for others, based on physician judgment) is appropriate to limit the severity of the event and to reduce the risk of recurrence in susceptible individuals.

The most common cutaneous events during daclizumab use were dermatitis, eczema, and rashes, which were manageable with treatment, including topical and/or systemic steroids, and treatment discontinuation. Some cases were serious and had features of a delayed-type hypersensitivity reaction. These cases typically presented with a more generalized, diffuse rash, and some cases required multiple courses of corticosteroids. While the most serious cases could be a source of significant discomfort to patients, the integrity of the skin was preserved and none of the events were directly life-threatening. Overall, the use of corticosteroids appeared to result in rapid improvement of many of the more serious cases. Over time, events generally resolved or substantially improved without permanent injury to the skin.

Infections were composed mainly of upper respiratory tract, urinary tract, and viral infections typical of those seen in a non-immunocompromised MS population. While the incidence of both minor and serious infections was increased during daclizumab use, the pattern and outcome of the events indicated that the ability of the subjects' immune system to effectively respond to the infection was preserved. Overall, the infections that have occurred during daclizumab use have been manageable with standard care, and the incidence of infections necessitating discontinuation of study treatment has been <1%.

Upon comprehensive review of all information available, across all studies, 6 subjects being treated with daclizumab attempted suicide. Two of these did not have a prior history of depression. Three serious

adverse events of depression were noted following treatment with daclizumab and depression was found as a safety concern and reflected in the risk minimization activities.

Overall, the safety profile of daclizumab includes several serious risks, including elevations of serum transaminases and hepatic injury, cutaneous events, infections, and depression. Based on the known immunomodulatory effect of daclizumab and the pattern of AEs observed, including response to treatment, an immune-mediated mechanism was implicated in some of these events. During the development program, procedures were developed in conjunction with experts to enable early identification and management of these risks, and were tested during the clinical studies. These procedures can be translated into the clinical setting and used to provide guidance to prescribers. With appropriate physician and patient education and clinical vigilance, the risks associated with daclizumab can be managed by awareness and early recognition of developing risks, standard medical care, and treatment discontinuation.

Uncertainty in the knowledge about the unfavourable effects

The hepatic failure risk, although more frequent at starting of treatment, is not eliminated when the patient is in maintenance phase. The relevance of cutaneous disorders may have different value from patient to patient. Serious cutaneous adverse reactions are frequent and may require repeated corticosteroid use, which may result in skin atrophy or long-term adverse events.

Daclizumab has an impact over the immune system and the body response to external biological agents. Increased infections are very relevant, even as compared to IFN. Usually the risk of having a severe or disabling infection is time dependent. Therefore, this risk will increase as treatment duration progresses. Although no PML case has been reported with daclizumab, severe lymphopenia which is a known risk factor for the emergence of PML, has occurred in some patients.

Effects table

Effect	Short Description	Unit	Treatment daclizumab 150 mg	Control Placebo	Control IFN β-1a 30 µg	Uncertainties/ Strength of evidence	Refs
Favourable Effects							
ARR	Relapses per year	Rate	0.211 (0.15, 0.29)	0.458 (0.37,0.57)	-	The effect is robust, supported by sensitivity and subgroup analyses	1
		Rate	0.212 (0.19, 0.24)		0.393 (0.35, 0.44)		2
12-week SDP	Estimated proportion with 12-week sustained increase in EDSS (W52)	%	0.059	0.133	-	Hazard ratio=0.43 (0.21, 0.88) Effect is statistically and clinically significant	1

Effect	Short Description	Unit	Treatment daclizumab 150 mg	Control Placebo	Control IFN β-1a 30 µg	Uncertainties/ Strength of evidence	Refs
	Estimated proportion with 12-week sustained increase in EDSS (W96)	%	0.120	-	0.143	Hazard ratio=0.84 (0.66, 1.07) Trend was positive but not statistically significant with the prespecified analysis	2
24-week SDP	Estimated proportion with 24-week sustained increase in EDSS (W52)	%	0.026	0.111	-	Hazard ratio=0.24 (0.09, 0.63) Effect is statistically and clinically significant	1
	Estimated proportion with 24-week sustained increase in EDSS (W96)	%	0.092	-	0.121	Hazard ratio=0.73 (0.55, 0.98) p=0.0332 Effect is statistically and clinically significant	2
T2 hyperintense lesions	New or newly enlarging T2 hyperintense (W52)	Adjusted mean	2.42 (1.96, 2.99)	8.13 (6.65, 9.94)	-	Percent reduction=70.2% p<0.0001	1
	New or newly enlarging T2 hyperintense (W96)	Adjusted mean	4.31 (3.85, 4.81)	-	9.44 (8.46, 10.54)	Percent reduction=54.4% p<0.0001	2
Gd-enhancing lesions	Adjusted mean number of new Gd lesions (week 8 to 24)	Adjusted mean	1.46 (1.05, 2.03)	4.79 (3.56, 6.43)	-	Percent reduction=69.5% p<0.0001	1
	Adjusted mean number of new Gd lesions (W96)	Mean	0.4	-	1.0	Odds ratio=0.25 (0.20, 0.23) p<0.0001	2

Effect	Short Description	Unit	Treatment daclizumab 150 mg	Control Placebo	Control IFN β-1a 30 µg	Uncertainties/ Strength of evidence	Refs
MSIS-29 physical score	Percentage of subjects with a significant worsening at Week 52	%	20.4	31.6	-	Odds ratio=0.56 (0.35, 0.88) P= 0.0125	1
	Percentage of subjects with a significant worsening at Week 48	%	17		20	Odds ratio=0.83 (0.65, 1.06) P= 0.1329	2

Unfavourable Effects							
Hepatic events	Incidence of hepatobiliary events	%	3%	2%		SOC	1
		%	16%	-	14%	SMQ	2
Elevated liver enzymes	Elevation > 5 ULN	%	4%	<1%	-	Increased risk over comparator. Monthly monitoring required up to 4 months after treatment is stopped	1
		%	6%	-	3%		2
CD4 count	Number of subjects with post-baseline value <400 cells/mm^3	N (%)	186 (22)		141 (17)	The decrease in CD4 is more pronounced with daclizumab than with IFN β-1a	2
	Number of subjects with post-baseline value <200 cells/mm^3	N (%)	20 (2)		10 (1)		2
Infections	Incidence of infections	%	50%	44%	-	Increased incidence over IFN β-1a	1
		%	65%	-	57%		2
Cutaneous reactions	Incidence of cutaneous reactions	%	18%	13%	-	Increased over placebo	1
		%	37%	-	19%	Increased over IFN β-1a	2
Depression	Incidence of depression	%	7%	3%	-	SMQ Increased over placebo	1
		%	11%	-	10%	SMQ	2

Abbreviations: ARR: Annualized Relapse Rate; SDP: sustained disability progression; MSIS (29): Multiple sclerosis impact scale physical score; Refs: References; W: week; ULN: upper limit of normal.

Notes: 1: study 205MS201; 2: study 205MS301

Benefit-risk balance

Importance of favourable and unfavourable effects

There are several factors that may distinguish daclizumab from current therapies and that enable it to address current gaps in therapeutic options for RMS patients.

- Daclizumab is the first MS therapy whose primary mechanism of action is related to the modulation of IL-2 signaling, and its immunologic effects are reversible in a time frame consistent with its serum half-life.
- Daclizumab provides superior efficacy to IM IFN β-1a, currently one of the most widely used treatments for RMS, and the efficacy of daclizumab was evident across the spectrum of the RMS study populations with respect to key factors such as prior treatment history, level of MS inflammatory activity, and EDSS range at baseline. Daclizumab was significantly effective versus placebo and versus IM IFN β-1a in subjects with highly active and less active subgroups .
- Daclizumab will be the first approved MS therapy that has a monthly SC dosing regimen.

RMS patients with highly active MS are at elevated risk for long-term disability progression, and achieving early and complete control of MS activity with DMTs is currently recommended to provide a patient with the best opportunity to preserve function. High-efficacy DMTs are the mainstay of treatment for these patients, but their response to any individual treatment is variable, and therefore it is beneficial for physicians to have several treatments with differentiated mechanisms of action from which to select and tailor therapy.

For patients with active MS and who need a high-efficacy MS therapeutic but have known risk factors for the serious adverse effects of other MS therapies that have shown superior efficacy to IFN β-1a (e.g., patients who are JCV positive [in the case of natalizumab] or patients with cardiac disease [in the case of fingolimod]), or for those patients who are concerned about long-term immunosuppression and do not want to use a potentially irreversible therapy (such as alemtuzumab), daclizumab provides atreatment alternative although it should be noted that no information is available as for the risk of PML following treatment with Zinbryta.

RMS patients with less active forms of MS may also benefit from high-efficacy MS therapies considering the present therapeutic goal of eliminating MS activity as completely as possible to preserve function over the long term.

Benefit-risk balance

Discussion on the benefit-risk balance

The CHMP considers that daclizumab has shown statistically and clinically robust data in patients suffering from Relapsing Multiple Sclerosis. The clinical and MRI effect seen with the treatment was reproduced in several studies over up to 3 years and it was established that maintenance of treatment beyond one year was beneficial. The most significant adverse events relate to hepatic injury and elevated hepatic enzymes, infections, cutaneous reactions and depression.

The risk of hepatic injury and elevated liver enzymes is clear and monthly monitoring of liver enzymes is required during treatment and amendments have been made in the Product Information documents to guide monitoring of hepatic function. Monitoring of white blood cells and a warning regarding cases of tuberculosis in patients treated with daclizumab has also been implemented, and the present risk minimisation strategies are considered sufficient.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zinbryta in the treatment of adult patients with relapsing forms of Multiple sclerosis is favourable, and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Hepatic Risk Management Guide, Patient Card

Prior to launch of Zinbryta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

Objective and rationale:

To educate patients and physicians about the risk of severe hepatic injury and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

Proposed action:

The Hepatic Risk Management Guide will contain information for the physician on the risk of elevations in liver enzyme levels and severe liver injury in patients treated with Zinbryta, as well guide the physician/patient discussion around hepatic risk and the measures to manage this risk. The physician should discuss the risk of hepatic injury with the patient and provide them with a Patient Card.

The Patient Card informs patients of the risk of severe hepatic injury, and the possible symptoms, so that they are aware of situations in which they should contact a physician in a timely manner. In addition, the Patient Card explains the need for monitoring of liver function and educates the patient on the importance of adherence to their monthly blood tests

The Patient Card is designed to enable the physician to present patient-friendly information about Zinbryta to a patient at the time Zinbryta is prescribed. It will focus on the potential for severe hepatic injury with Zinbryta, and will also include information about symptoms of liver injury and instructions about monthly liver function monitoring.

- **Obligation to complete post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers by consensus that daclizumab is not qualified as a new active substance as significant differences in properties with regard to safety and/or efficacy from the previously authorised substance due to differences in molecular structure, nature of source materials or manufacturing process were not warranted.