Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare Pharmaceuticals Inc.	
Study Number:	91656 (309363)	NCT00459667
Study Phase:	IIIb	
Official Study Title:	International, multi-center, Phase IIIb study of subcutaneous every-other-day treatment of subjects with relapsing multiple sclerosis with (Phase A) double-blind Betaseron/Betaferon 250 µg or 500 µg or open-label Betaseron/Betaferon 250 µg and (Phase B) open-label Betaseron/Betaferon 500 µg BEYOND Follow-up study (BEYOND = Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose).	
Therapeutic Area:	Neurology	
Test Product		
Name of Test Product:	Interferon beta-1b (Betaseron, BAY86-5046)	
Name of Active Ingredient:	Recombinant interferon beta-1b (IFNB-1b)	
Dose and Mode of Administration:	500 µg every other day (e.o.d.), subcutaneous (s.c.) administration.	
Reference Therapy/Placebo		
Reference Therapy:	Phase A only: Recombinant interferon beta-1b (IFNB-1b, Betaferon/Betaseron)	
Dose and Mode of Administration:	250 µg e.o.d., s.c. administration	
Duration of Treatment:	Treatment with test product was continued until results of the BEYOND study (study 306440) became available (end of Phase A), or until IFNB-1b 500 µg was available to the subjects in their respective countries, or at the maximum for 2.5 years after the start of Phase B. Reference therapy: Up to 12 months (subject to the time of unblinding of BEYOND study)	
Studied period:	**Date of first subjects' first visit:**	03 MAY 2007
	Date of last subjects' last visit:	14 MAR 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 08 MAR 2007) to the original study protocol became necessary for Finnish centers of the study. The local amendment followed a request of the ethics committee of the Finnish Ministry of Social Affairs and Health that decided not to allow enrollment of the following subject groups into the BEYOND Follow-up study 309363: • Randomization to Copaxone during the preceding BEYOND study 306440 or	

	• Premature end of study medication (EOSM) during the preceding BEYOND study 306440.
Study Centre(s):	This study was conducted in a total of 173 centers with at least 1 randomized subject in 25 countries.
Methodology:	The study was designed to have two consecutive phases (Phase A and B) (Follow-up of study 306440 [BEYOND], which compared safety and efficacy of IFNB-1b 250 µg, IFNB-1b 500 µg, and Copaxone 20 µg over 104 weeks). **Phase A:** • Double-blind comparison of safety and tolerability of IFNB-1b 250 µg and IFNB-1b 500 µg, both given s.c. and e.o.d. • Open-label assessment of safety and tolerability of IFNB-1b 250 µg s.c. and e.o.d. in subjects pre-treated with Copaxone or with premature end of study medication (EOSM) in the BEYOND study **Phase B:** • Open-label assessment of safety and tolerability of IFNB-1b 500 µg s.c. and e.o.d. • Treatment duration of Phase B (whichever period was shorter): From end of Phase A until availability of IFNB-1b 500 µg to the subjects in their respective countries or 130 weeks post start of Phase B at the maximum. After availability of results of the BEYOND study, it was decided not to start Phase B.
Indication/ Main Inclusion Criteria:	Indication: Relapsing-remitting multiple sclerosis (RRMS) Main Inclusion Criteria: Female and male subjects who completed the previous study 306440 (BEYOND study) successfully (i.e., no premature end of study [EOS] in the BEYOND study); with diagnosis of relapsing multiple sclerosis (MS) (i.e., including secondary progressive MS [SPMS] with superimposed relapses).
Study Objectives:	**Overall:** To further increase knowledge on safety and tolerability of treatment with IFNB-1b 500 µg. **Primary:** To increase the knowledge on the safety and tolerability profile of IFNB-1b 500 µg. **Secondary:** To increase knowledge of neutralizing activity to INFB-1b and on patient reported outcomes (PRO).
Evaluation Criteria:	**Efficacy (Primary):** Not applicable

	Efficacy (Secondary): Not applicable **Safety:** Primary variable: Frequencies of the following events: • Flu-like syndrome • Injection-site reactions • Liver enzyme elevations • Hematological abnormalities All adverse events (AEs); clinical laboratory; vital signs; electrocardiogram (ECG); Beck Depression Inventory-2nd edition (BDI-II)
	Other: • Neutralizing antibodies (NAbs) • Functional assessment of multiple sclerosis (FAMS) • European Quality of Life – 5 dimensions (EQ-5D)
Statistical Methods:	**Efficacy (Primary):** Not applicable **Efficacy (Secondary):** Not applicable **Safety:** Descriptive statistics (including 95% confidence intervals) were provided for the differences in proportions of subjects experiencing each of the primary safety variables in the two treatment groups in the double blind part of Phase A. Also, similar descriptive statistics with 95% confidence intervals were provided for the primary safety variables in the open label part of Phase A. Phase B was not initiated according to the criteria described in the protocol.
	Other: NAbs: The measurements of NAbs were converted into a dichotomous variable (positive/negative) based on the following cut-off value for NAb titers (< vs ≥): • neutralizing titer 20, • neutralizing titer 100, and • neutralizing titer 400 FAMS and EQ-5D: The variables derived from the PRO assessments, i.e. FAMS and EQ-5D, were not analyzed due to the termination of the study before initiation of Phase B.
Number of Subjects:	Planned: Phase A: approximately 1880; Phase B: ca. 1300

	Analyzed Safety analysis set (SAF): Phase A: IFNB-1b 500 µg-group: 586 IFNB-1b 250 µg-group: 645 IFNB-1b 250 µg-group (Open-label arm with subjects who were administered Copaxone and subjects who had prematurely discontinued medication during the BEYOND study): 180 Phase B: Not performed

Study Results

Results Summary — Subject Disposition and Baseline

For analyses, the SAF, comprising all subjects to whom at least one dose of study medication was dispensed, was used (number/percentage of subjects). Only data from subjects not meeting this definition were listed. Table 1 summarizes the number of subjects in the full analysis set (FAS) and SAF.

Table 1: Subjects in FAS and SAF

	IFNB-1b 500 µg		IFNB-1b 250 µg		IFNB-1b 250 µg*		Overall	
Full analysis set (FAS)	592	100.0%	647	100.0%	181	100.0%	1420	100.0%
Safety analysis set (SAF)	586	99.0%	645	99.7%	180	99.4%	1411	99.4%

* Open-label arm with subjects who were administered Copaxone and subjects who had prematurely discontinued medication during the BEYOND study.

In the BEYOND follow-up study, there were no relevant group differences in any of the demographic parameters. Overall, 972 subjects (68.9%) were female. Mean age was 35.9 ± 9.3 years. The majority of subjects were between 18 and 65 years of age (99.1%) and of Caucasian origin (91.9%). Demographics in this study were similar to those reported for the preceding BEYOND study.

The subjects' history of MS had already been recorded for the preceding BEYOND study. Therefore, no separate recordings were scheduled for this BEYOND Follow-up study. In general, the various aspects of MS history were similar between the treatment groups full analysis set (FAS) of the BEYOND study.

A total of 1420 subjects (FAS) participated in the BEYOND Follow-up study, and study medication was dispensed to 1411 subjects (SAF). Table 2 describes premature discontinuations (recorded as number/percentage of subjects):

Table 2: Premature discontinuations in SAF

	IFNB-1b 500 µg		IFNB-1b 250 µg		IFNB-1b 250 µg*		Overall	
Safety analysis set (SAF)	586	100%	645	100%	180	100%	1411	100%
Discontinuations from study course	19	3.2%	34	5.3%	15	8.3%	68	4.8%
Discontinuations from study drug	32	5.5%	42	6.5%	19	10.6%	93	6.3%

* Open-label arm with subjects who were administered Copaxone and subjects who had prematurely discontinued medication during the BEYOND study.

Results Summary — Efficacy
Not applicable
Results Summary — Safety

In summary, the findings of this study were consistent with the known safety profile of IFNB-1b.

Any AE

Overall, 72.7% (IFNB-1b 250 µg) to 77.6% (IFNB-1b 500 µg) of subjects were affected by at least one AE.

In the IFNB-1b 500-µg group, the most commonly recorded AEs were "fatigue" (15.2%, observed at least once), followed by "injection site reaction" (13.7%), "influenza-like illness" and "headache" (both 12.3%). The AE profiles of the other groups were slightly different, with "headache" (13.8%), "fatigue" (13.8%), "injection site erythema" (11.3%), and "multiple sclerosis relapse" (11.0%) as the most commonly recorded AEs for the IFNB-1b 250-µg group and "influenza-like illness" (20.6%), "headache" (14.4%), "depression" (12.8%), and "fatigue" (12.8%) as the most commonly recorded AEs for the IFNB-1b 250-µg group*

(*Open-label arm with subjects who were administered Copaxone and subjects who had prematurely discontinued medication during the BEYOND study).

Causal relationship of AEs

Overall, the proportions of subjects with at least one record of any AE with the investigator's classification as being treatment-related were 47.8% (IFNB-1b 250 µg), 55.6% (IFNB-1b 500 µg), and 56.1% (IFNB-1b 250 µg*).

All IFNB-1b groups had a comparable AE profile, with the most commonly recorded related AE being "injection site reaction" followed by "influenza-like illness", "injection site erythema", and "headache". Incidences of "injection site reaction", "influenza-like illness", and "injection site erythema" in the IFNB-1b 500 µg group were slightly higher than in the other groups.

In the IFNB-1b 250 µg group*, clearly higher incidences were recorded for the related AEs "influenza-like illness", "headache", "alanine aminotransferase increased", "aspartate aminotransferase increased", "myalgia", "pyrexia" and "neutrophil count decreased" compared to the IFNB-1b 250 µg and the IFNB-1b 500 µg group. Because subjects in the IFNB-1b 250 µg group* were previously treated with Copaxone they were likely to show this AE pattern, as flu-like syndromes and elevated liver enzymes were known to usually occur early after initiation of IFNB-1b-treatment.

Intensity of AEs

About 70% of all subjects had AEs with a maximum intensity of either mild or moderate. The proportion of subjects with at least one AE of severe intensity ranged between 6.0% (IFNB-1b 250 µg) and 7.2% (IFNB-1b 500 µg). However, no individual AE was recorded as severe in more than 2.8% of the subjects of any group; the majority of severe events was recorded in ≤1% of the subjects of any group.

Frequency: "Flu-like syndrome (all associated preferred terms [PTs])"

The incidence of any "flu-like syndrome" was approximately twice as high in IFNB-1b 250 µg*- treated subjects compared to the IFNB-1b 500 µg group or the IFNB-1b 250 µg group

(31.1% versus 17.4% and 15.8%, respectively); the most frequently recorded term was "influenza-like illness". Subjects previously treated with Copaxone were likely to show this AE pattern, as flu-like symptoms were known to predominantly occur early after initiation of IFNB-1b-treatment.

Frequency: "Injection site reactions (all associated PTs)"

Higher proportions of subjects affected by any injection site reaction were recorded for the IFNB-1b 500 µg and the IFNB-1b 250 µg group* (31.7% each) whereas a slightly lower proportion (26.2%) of IFNB-1b 250 µg treated subjects was affected. Across all three treatment groups, the most frequently recorded types of injection site reaction were "injection site reaction" and "injection site erythema". Again, besides a dose-relatedness of injection site reactions, these symptoms predominantly occurred at the beginning of IFNB-1b-treatment and decreased over time.

Frequency: "Liver enzyme elevations (all associated PTs)"

The highest proportion of subjects affected by any "liver enzyme elevation" was recorded for the IFNB-1b 250 µg group* (6.7%). In the IFNB-1b 500 µg group (4.6%) and the IFNB-1b 250 µg group (2.9%), lower incidence rates of liver enzyme elevations were reported. Two subjects from the IFNB-1b 250 µg group discontinued treatment prematurely due to liver-related AEs.

Frequency: "Hematological abnormalities (all associated PTs)"

Decreased hemoglobin levels and decreased lymphocyte counts qualified as AEs were reported in the IFNB-1b 500 µg and IFNB-1b 250 µg groups only, with higher incidences of decreased lymphocyte counts in the 500 µg IFNB-1b group**.** Higher incidences of decreased neutrophil and white blood cell counts were detected in both 250-µg groups whereas decreased platelets were most frequently reported in the 500 µg IFNB-1b group. Two subjects from the IFNB-1b 250 µg group and one subject from the IFNB-1b 500 µg group discontinued treatment prematurely due to hematology-related AEs.

Deaths, non-fatal serious adverse events (SAEs) and other significant AEs

No deaths were recorded during the study course.

Non-fatal SAEs

The proportion of subjects affected by at least one SAE ranged between 1.9% (IFNB-1b 500 µg) and 3.3% (IFNB-1b 250 µg*).

Any SAE in any IFNB-1b group occurred only once, resulting in incidences of 0.2% to 0.6% with the exception of "elective surgery", which was recorded in 2 subjects (1.1%) of the IFNB-1b 250 µg* group. One subject each in the IFNB-1b 500 µg group and the IFNB-1b 250 µg* group as well as two subjects in the IFNB-1b 250 µg group reported a total of 5 drug-related SAEs during the course of this study.

Premature termination of study drug due to an AE

Overall, the proportion of subjects with premature termination of study drug due to an AE ranged between 1.5% (IFNB-1b 500 µg) and 4.4% (IFNB-1b 250 µg*). Events typically associated with IFNB-1b treatment, such as flu-like symptoms ("influenza-like illness") and local reactions ("injection site reactions") were predominantly reported in the IFNB-1b 500 µg group whereas laboratory-related events like liver enzyme elevations were notably more frequent in the IFNB-1b 250 µg group*.

Clinical laboratory evaluations

The overall incidence of any liver enzyme elevations was very low. The highest proportions of subjects affected were recorded for the IFNB-1b 500 µg group compared to the IFNB-1b 250 µg group (0.9% versus 0.3%).

The only notable "hematological abnormality" was decreased lymphocyte counts. Concerning AEs related to "hematological abnormalities", the highest proportion of subjects with this finding were recorded for the IFNB-1b 500 µg group compared to the IFNB-1b 250 µg group (1.0% versus 0.3%). No hematological abnormalities were detected in the IFNB-1b 250 µg* group.

Liver enzyme elevation occurred more frequently in the IFNB-1b 500 µg and IFNB-1b 250 µg* groups than in the IFNB-1b 250 µg group, with higher incidences in the IFNB-1b 250 µg* group than in the IFNB-1b 500 µg group. Subjects previously treated with Copaxone were likely to show this AE pattern, as elevated liver enzymes were known to predominantly occur early after initiation of IFNB-1b-treatment. Elevations in alanine aminotransferase/glutamic pyruvate transaminase (ALT/GPT) were usually seen with associated elevations in aspartate transaminase/glutamic oxaloacetic transaminase (AST/GOT). Grade-3 but no Grade-4 elevations were found in the IFNB-1b 500 µg and IFNB-1b 250 µg* groups only. These findings are in line with previous IFNB-1b trials.

Hematological parameters below the expanded reference ranges occurred more frequently in the IFNB-1b 500 µg and IFNB-1b 250 µg groups than in the IFNB-1b 250 µg group*, with higher incidences in the IFNB-1b 250 µg group than in the IFNB-1b 500 µg group. Values below the expanded reference ranges for leukocytes were often seen in association with low neutrophil levels. The majority of Grade-3 toxicities for leukocyte, neutrophil and lymphocyte counts as well as hemoglobin were reported at single occasions at any time during the study. No Grade-4 elevations were reported. These findings are in line with previous IFNB-1b trials.

Overall, a tendency toward earlier occurrences and higher incidences of decreased leukocyte, neutrophil, and lymphocyte counts compared to baseline were notable for the IFNB-1b 250 µg group* during the study. Nevertheless, no group specific differences for these parameters were detected at EOS. No notable changes from baseline were detectable for other haematological parameters throughout the study.

Lipid parameters as well as other serum chemistry parameters or urinalysis parameters did not deviate significantly from the known safety profile of IFNB-1b.

In all IFNB-1b groups, there was a slight trend towards a post-baseline increase of median serum levels of T4. There was an increase of thyroid stimulating hormone (TSH) levels in the IFNB-1b 500 µg and, more prominently, IFNB-1b 250 µg* group. A trend to higher frequencies of thyroid-related AEs was notable for the IFNB-1b 500 µg group. The results showed no relevant differences to previous findings.

Blood pressure

For systolic and diastolic blood pressure, all treatment groups showed mean increases at EOS of about 2 mmHg and 1 mmHg, respectively, without conclusive group differences. As these increases were not reflected by the median values in all treatment groups, they were most likely attributable to individual outliers. No group differences were noted for blood pressure related AEs. None of those AEs, as like as any other AEs related to vital signs, led to study drug withdrawal. Overall, no specific pattern of clinically relevant findings of vital sign parameters or ECG recordings can be attributed to any IFNB-1b treatment.

Beck depression index (BDI-II)

The Beck Depression Inventory-II as a self-administered rating inventory measuring characteristic attitudes and symptoms of depression did not reveal relevant group differences. No reasonable statement can be made concerning unfavorable (≤13 to ≥14) or favorable (≥14 to ≤13) shifts during the course of the study within the treatment groups.

Other safety variables

No relevant findings were found for the other safety evaluations, including pulse, body temperature, and 12-lead ECG.

* Open-label arm with subjects who were administered Copaxone and subjects who had prematurely discontinued medication during the BEYOND study.

Results Summary — Other

Neutralizing antibodies

At the EOS visit, overall positive NAb titers were observed for 23.1% of subjects for titers ≥20, 12.8% of subjects for titers ≥100, and 8.0% for titers ≥400. In general, there tended to be more IFNB-1b 500 µg subjects with positive titers (26.6%, 16.5%, and 10.8%, respectively) followed by subjects receiving IFNB-1b 250 µg (21.7%, 12.4%, and 6.1%). As neutralizing antibodies generally occur with a considerable lag time after initial IFNB-1b exposure, subjects who did receive open-label glatiramer acetate (Copaxone) or prematurely discontinued during the BEYOND study and switched to open-label IFNB-1b 250 µg treatment showed the lowest prevalence of positive titers for all plasma dilutions (16.6%, 2.5%, and 0%). No further evaluations with respect to individual positive titers and reconversion status were performed in this study.

The variables derived from the subject-reported outcomes assessments, i.e., FAMS and EQ-5D, were not analyzed due to the termination of the study before start of Phase B.

Conclusion(s)

- In this study, both IFNB-1b doses were well tolerated irrespective of glatiramer pre-treatment as indicated by the low rate of premature terminations of study medication due to AEs.
- Safety findings were consistent with the known safety profiles of IFNB-1b.
- As known for IFNB-1b, the incidence of flu-like symptoms, injection site reactions, and liver abnormalities was higher after initiation of IFNB-1b therapy.
- A small dose-dependent trend towards higher incidences in IFNB-1b 500 µg subjects was noted for injection-site reactions, liver and hematological abnormalities as already shown in the BEYOND study.

Publication(s):	None		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin Deutschland
Sponsor in Germany (if applicable)	
Legal Entity Name	Bayer HealthCare AG
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List of Investigational Sites

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2	Fundacion FACENE	Larrea 1035, PB B	C1117ABE	Buenos Aires	ARGENTINA
3	Hospital Británico	Perdriel 74 (C1280) Capital Federal Buenos Aires	C1280AEB	Buenos Aires	ARGENTINA
4	Hospital Militar de Cordoba	Avenida Cruz Roja Argentina 1174	X5000HGX	Cordoba	ARGENTINA
5	Instituto de Neurociencias de Rosario	San Lorenzo 3598		Rosario	ARGENTINA
6	Policlinica Bancaria	Gaona 2197 Ala Oeste Piso 2 Buenos Aires	C1416CRJ	Buenos Aires	ARGENTINA
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30	Montreal Neurological Hospital	3801 University avenue Montreal, Quebec H3A 2B4	H3A 2B4	Montreal	CANADA
31	Ottawa Headache Centre West	Ottawa Headache Centre West 1 Centerpoint Drive, Suite 407 Nepean, Ontario K2G 6E2 Canada	K2G 6E2	Nepean	CANADA
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62	Universitätsklinikum Giessen und Marburg	Zentrum für Neurologie und Neurochirurgie Neurologische Klinik Am Steg 14	35392	Gießen	GERMANY
63	Universitätsklinikum Hamburg Eppendorf (UKE)	Klinik und Poliklinik für Neurologie Martinistr. 52	20246	Hamburg	GERMANY

64	Universitätsklinikum Heidelberg	Neurologische Universitätsklinik Im Neuenheimer Feld 400	69112	Heidelberg	GERMANY
65	Universitätsklinikum Münster	Klinik und Poliklinik für Neurologie Albert-Schweitzer-Str. 33	48149	Münster	GERMANY
66	Universitätsmedizin der Georg-August-Universität Göttingen	Zentrum Neurologische Medizin Robert-Koch-Str. 40	37099	Göttingen	GERMANY
67	Vivantes Klinikum Spandau	Klinik für Neurologie und Zentrum für Schwerst-Schädel-Hirnverletzte Neue Bergstr. 6	13585	Berlin	GERMANY
68	AHEPA University General Hospital of Thessaloniki	S. Kyrikidi street 1 54636 Thessaloniki	54636	Thessaloniki	GREECE
69	G. Gennimatas General State Hospital of Athens	154, Mesogion Av.	11527	Athens	GREECE
70	Borsod County Hospital	Borsod County Hospital Szentpeteri kapu 72-76 3501 Miskolc	3501	Miskolc	HUNGARY
71	Pecsi TE Neurologiai Klinika	Neurologiai Klinika Ret u 2.	7623	Pecs	HUNGARY
72	Peterfy Sandor utcai Korhaz - Rendelointezet	Dept. of Neurology Peterfy s. u. 8-20	1076	Budapest	HUNGARY

73	Petz Aladar Megyei Korhaz	Petz Aladar Megyei Oktato Hospital Vasvari Pal u 2-4 H-9024 Gyor	9024	Györ	HUNGARY
74	Uzsoki utkai Korhaz	Uzsoki Hospital Dept. of Neurology Uzsoki u. 29 1145 Budapest	1145	Budapest	HUNGARY
75	Zala Megyei Korhaz	Zala Megyei Korhaz Neurologiai Osztaly Zrinyi u. 1	H-8900	Zalaegerszeg-Pozva	HUNGARY
76	Adelaide & Meath Hospital	FDVH Annex Adelaide & Meath Hospital incorp. the National Children's Hospital Tallaght		Dublin	IRELAND
77	Beaumont Hospital	Beaumont Road Dublin 9	9	Dublin	IRELAND
78	Cork University Hospital	Wilton Cork		Cork	IRELAND
79	St Vincents University Hospital	Elm Park Dublin 4	4	Dublin	IRELAND
80	Assaf Harofeh Medical Center	Zerifin	70300	Zerifin	ISRAEL
81	Barzili Medical Center	3, Hahistadrut Street	78278	Ashkelon	ISRAEL
82	Bnai Zion Medical Center	Golomb 47 St. POB 4940	31048	Haifa	ISRAEL
83	Hebrew University - Hadassah Medical School	Hadassah Medical School Kiryat Hadassah P. O. B. 12000	91120	Jerusalem	ISRAEL

84	Sheba Medical Center	Tel Hashomer 52621 Chaim Sheba Medical Center	52621	Tel Hashomer	ISRAEL
85	Sourasky Medical Center	6 Wetzman st.	64239	Tel-Aviv	ISRAEL
86	A.O. di Padova	Via Giustiniani, 2	35128	Padova	ITALY
87	A.O.U. Careggi	.	50134	Firenze	ITALY
88	Ospedale San Raffaele	Via Olgettina, 48	20132	Milano	ITALY
89	Ospedale Sant'Andrea	Via di Grotta Rossa, 1035	00189	Roma	ITALY
90	Neurology Departmant of Latvian	MS Centre Maritime Medicine Centre Vecmilgravis Hospital 5.lin. 26 Vecmilgravis	LV-1015	Riga	LATVIA
91	Amphia Ziekenhuis, locatie Langendijk	Molengracht 21 4818 CK Breda	4819 EV	Breda	NETHERLANDS
92	Multiple Sclerose Centrum Nijmegen	Heiweg 97 6533 PA NIJMEGEN	6533 PA	Nijmegen	NETHERLANDS
93	Orbis Medisch Centrum	Walramstraat 23 6131 BK SITTARD	6131 BK	Sittard	NETHERLANDS
94	Haukeland universitetssjukehus, Bergen	Haukeland universitetssjukehus, Bergen Jonas Liesvei 65 N-5021 Bergen NORWAY	N-5021	Bergen	NORWAY

95	Centralny Szpital Kliniczny AM	Katedra i Klinika Neurologii Akademii Medycznej ul. Banacha 1a 02-097 Warszawa	02097	Warszawa	POLAND
96	II Klinika Neurologii	II Klinika Neurologii ul. Sobieskiego 9 02-957 Warszawa	02957	Warszawa	POLAND
97	Katedra i Klinika Neurologii Sl.A.M	ul. Medykow 14	40752	Katowice	POLAND
98	SP Szpital Kliniczny nr 2	Dluga 1/2 61-848 Poznan	61848	Poznan	POLAND
99	SP Szpital Kliniczny nr 5	Akademii Medycznej we Wroclawiu Katedra i Klinika Neurologii ul. Traugutta 118 50-420 Wroclaw	50420	Wroclaw	POLAND
100	Szpital im. N. Barlickiego	Akademia Medyczna w Lodzi ul. Kopcinskiego 22 PL 90-153 Lodz	90153	Lodz	POLAND
101	Wojewodzki Szpital Specjalistyczny im. M. Kopernika	Oddzial Neurologiczny ul. Nowe Ogrody 1/6 80-803 Gdansk	80-803	Gdansk	POLAND
102	1st Medical Academy Municipal Hospital N61	City Clinical Hospital Dovatora ul. 15 118089 Moskva	118089	Moskva	RUSSIA

103	1st Pirogov Clinical Hospital	Russian State Medical University Department of Neurology and Neurosurgery Leninsky prospekt, dom 8 / korpus 8 117049 Moskva	117049	Moskva	RUSSIA
104	City Hospital N 33	Municipal City Hospital No. 33 Department of Neurology 54 prospect Lenina 603076 Nizhy Novgorod	603076	Nizhy Novgorod	RUSSIA
105	Institute of Brain of Russian	Institute of Brain of Russian Academy of Medical Sciense Ulitsa Akademika Pavlova, dom 12	197376	St. Petersburg	RUSSIA
106	Institute of Neurology of Russian Academy of Medical Science	Institute of Neurology Department of Neuroinfections Volokolamskoye shosse, dom 80 123367 Moskva	123367	Moskva	RUSSIA
107	Medical Military Academy	Medical Military Academy Neurology Department 2 Lesnoj pr.	194044	St. Petersburg	RUSSIA
108	MONIKI	ulitsa Shchepkina, dom 61/2 129110 Moskva	129110	Moskva	RUSSIA

109	Moskva City MS Center	Moskva City MS Center Ulitsa Dvintsev, dom 6 127018 Moskva	127018	Moskva	RUSSIA
110	Siberian District Medical Center	Kainskaya ul. 13	630007	Novosibirsk	RUSSIA
111	St. Petersburg Medical University n.a. Pavlov	Meditsinskii Universitet ulitsa Liva Tolstogo, dom 6/8 197022 Sankt-Peterburg	197022	Sankt-Peterburg	RUSSIA
112	Yaroslavl Medical Academy	Department of neurology and medical genetic Suzdalskoye shosse 39, floor 2	150039	Yaroslavl	RUSSIA
113	Klinicni center	University Medical Centre Ljubljana Division of Neurology Department of Neurology Zaloska 2 SI - 1525 Ljubljana	SI-1525	Ljubljana	SLOVENIA
114	Splosna Bolnisnica Marobor	Ljubljanska 5	2000	Maribor	SLOVENIA
115	Ciutat Sanitària i Universitària de Bellvitge	Secretaria de Consultas Externas Módulo 21- 2ª planta Feixa Llarga, s/n	08907	L'Hospitalet de Llobregat	SPAIN

116	Hospital Regional Carlos Haya	Hopital Universitario Virgen Macarena Complejo Hospitalario Carlos Haya Avda. Carlos Haya, s/n	29010	Malaga	SPAIN
117	Hospital Universitario Virgen de la Macarena	Avda. Dr. Fedriani, 3	41071	Sevilla	SPAIN
118	Akademiska Sjukhuset	Neurologkliniken Neurocentrum 751 85 Uppsala	751 85	Uppsala	SWEDEN
119	Danderyds sjukhus	Neurologmottagningen 182 88 Stockholm	182 88	Stockholm	SWEDEN
120	Inselspital Bern	Freiburgstrasse 4	3010	Bern	SWITZERLAND
121	Kantonsspital St. Gallen	Rorschacherstrasse 95	9007	St. Gallen	SWITZERLAND
122	City Clinical Hospital #4	Neurology Department Solomenskaya ul. 17	03110	Kiev	UKRAINE
123	Donetsk state medical university	Chair of Child and General Neurology Ilicha ul. 16	83003	Donetsk	UKRAINE
124	Institute of Neurology, Psychiatric and Narcology of AMSU	Academic Pavlov ul. 46	61068	Kharkiv	UKRAINE
125	Regional Clinical Hospital	Chernihivskaya ul. 7	79000	Lviv	UKRAINE
126	Advanced Neurosciences Institute	4230 Harding Road Suite 807-E	37205	Nashville	UNITED STATES
127	Axiom Clinical Research	2919 Swann Avenue Suite 401	33609	Tampa	UNITED STATES

128	Barrow Neurology Clinic	500 West Thomas Road Suite 300	85013	Phoenix	UNITED STATES
129	Baylor College	One Baylor Plaza, NB302 Houston, TX 77030	77030	Houston	UNITED STATES
130	Carolinas Medical Center	Carolinas Medical Center MS Center 1350 S. Kings Drive Charlotte, NC 28207	28207	Charlotte	UNITED STATES
131	Coastal Neurological Medical Group	9850 Genesee Avenue Suite 740	92037	La Jolla	UNITED STATES
132	Dr. Tamara Miller, MD	2121 E. Harmony Road	80528	Fort Collins	UNITED STATES
133	Duke University Medical Center	122 Baker House Box 3184	27710	Durham	UNITED STATES
134	East Bay Region Associates in Neurology	3000 Colby Street Suite 203 B	94705	Berkeley	UNITED STATES
135	Fort Wayne Neurological Center	2622 Lake Avenue	46805	Fort Wayne	UNITED STATES
136	George Washington University	Department of Neurology 2150 Pennsylvania Avenue NW Suite 7-404 Washington, DC 20037	20037	Washington	UNITED STATES
137	Henry Ford Health System	2799 West Grand Boulevard Detroit, MI 48202	48202	Detroit	UNITED STATES
138	Hospital of the University of Pennsylvania	University of Pennsylvania Medical Center 3 West Gates Building 3400 Spruce Street	19104	Philadelphia	UNITED STATES

139	Indiana University	MS Center 541 Clinical Drive, Room CL 292 Indianapolis, IN 46202	46202	Indianapolis	UNITED STATES
140	Integra Clinical Research, LLC	4242 Medical Drive Building 6, Suite 100	78229	San Antonio	UNITED STATES
141	Louisiana State University Medical Center	1501 Kings Highway	71130	Shreveport	UNITED STATES
142	Medical University of South Carolina	Neurology Department 96 Jonathan Lucas Street Suite 309 P.O. Box 250606	29425	Charleston	UNITED STATES
143	Mercy Ruan Neurology Clinic	1111 6th Avenue East Tower, Suite A-100	50314	Des Moines	UNITED STATES
144	Neurology Associates	19250 SW 65th Suite 155	97062	Tualatin	UNITED STATES
145	Neurology Associates, PA	Neurology Associates, P.A. 774 Christiana Road, Suite 201 Newark, DE 19713	19713	Newark	UNITED STATES
146	Neurology Associates, PA	Neurology Associates 301 North Maitland Avenue, Suite A-1 Maitland, FL 32751	32751	Maitland	UNITED STATES
147	Neurology Center of Fairfax, Ltd.	3020 Hamaker Court Suite 400	22031	Fairfax	UNITED STATES
148	Neurology Foundation, Inc.	2 Dudley Street Suite 555	02905	Providence	UNITED STATES

149	Neurology & Neurosurgery Associates of Tacoma, Inc.	915 6th Avenue, Suite 101 Tacoma, WA 98405	98405	Tacoma	UNITED STATES
150	Nevada Neurological Consultants, Ltd.	880 Seven Hills Drive Suite 200	89052	Henderson	UNITED STATES
151	North Central Neurology Associates	1809 Kress Street	35058	Cullman	UNITED STATES
152	Northwest NeuroSpecialists, PLLC	Northwest NeuroSpecialists, PLLC 5860 N La Cholla Boulevard, Suite 100 (Research) Tucson, AZ 85741	85741	Tucson	UNITED STATES
153	Ohio State University Medical Center	451 Means Hall 1654 Upham Drive Columbus, OH 43210	43210	Columbus	UNITED STATES
154	Riverhills Healthcare, Inc.	111 Wellington Place	45219	Cincinnati	UNITED STATES
155	Shepherd Center	2020 Peachtree Road, NW	30309-1465	Atlanta	UNITED STATES
156	St. Mary's/Duluth Clinic Health System	Duluth Comprehensive MS Center Maildrop - 5 AV 2 ME 400 East Third Street Duluth, MN 55805	55805	Duluth	UNITED STATES
157	SUNY at Stony Brook	SUNY - Stony Brook MS Comprehensive Care Center Health Sciences Center T12-020 Stony Brook, NY 11794	11794	Stony Brook	UNITED STATES

158	Tampa General Hospital	Clinical Research Center Harbourside Medical Tower Suite 370 4 Columbia Drive	33606	Tampa	UNITED STATES
159	University Neurologists, PSC	Dba Kentucky Neuroscience Research 601 South Floyd Suite 503	40202	Louisville	UNITED STATES
160	University of Alabama at Birmingham	Dept. of Neurology 619 South 19th Street, Suite 1205 JT	35294-7340	Birmingham	UNITED STATES
161	University of California Davis Medical Center	4860 Y Street Suite 3700	95817	Sacramento	UNITED STATES
162	University of California, San Francisco	UCSF Multiple Sclerosis Center 350 Parnassus Avenue, Suite 908 San Francisco, CA 94117	94117	San Francisco	UNITED STATES
163	University of Chicago Hospitals	Pritzker School of Medicine 5841 S. Maryland Avenue MC2030	60637	Chicago	UNITED STATES
164	University of Kansas Medical Center	3901 Rainbow Boulevard	66160	Kansas City	UNITED STATES

165	University of Medicine and Dentistry of New Jersey	University of Medicine and Dentistry of New Jersey Doctor's Office Center 90 Bergen Street, Suite 8100 Newark, NJ 07103	07103	Newark	UNITED STATES
166	University of Miami	University of Miami - Neurology Department of Neurology 1501 North West 9th Avenue Miami, FL 33136	33136	Miami	UNITED STATES
167	University of Nevada-Reno	Washoe Institute of Neurosciences 50 Kirman Ave. Suite 201	89509	Reno	UNITED STATES
168	University of New Mexico	The MIND Imaging Center 1201 Yale Boulevard NE Albuquerque, NM 87131-5281	87131-5281	Albuquerque	UNITED STATES
169	University of Pittsburgh Medical Center Health System	Lillian Kaufmann Building 3471 5th Avenue, Suite 811	15213	Pittsburgh	UNITED STATES
170	University of Rochester Medical Center	Department of Neurology 601 Elmwood Avenue Box 605, Room 68521	14642	Rochester	UNITED STATES
171	Virginia Mason Medical Center	Virginia Mason MS Center 1100 9th Avenue Seattle, WA 98101	98101	Seattle	UNITED STATES
172	Wake Forest University Medical Center	Department of Neurology Medical Center Boulevard Winston-Salem, NC 27157	27157	Winston-Salem	UNITED STATES

173	Winthrop-University Hospital	Clinical Trials Center 222 Station Plaza North, Suite 300 Mineola, NY 11501	11501	Mineola	UNITED STATES

Product Identification Information

Product Type	Biological product
US Brand/Trade Name(s)	Betaseron
Brand/Trade Name(s) ex-US	Betaseron, Betaferon
Generic Name	Interferon beta – 1b
Main Product Company Code	BAY86-5046
Other Company Code(s)	ZK 157046
Chemical Description	Recombinant protein
Other Product Aliases	

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