COVER PAGE

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Long-term surveillance of patients with multiple sclerosis to report progressive multifocal leukoencephalopathy and other serious opportunistic infections among patients treated with natalizumab

FINAL COMPARATIVE SAFETY REPORT 2024

Final report to the 31st of December 2024

In Prague, 31st March 2025

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CI	Confidence Interval
DLP	Data Lock Point
DMD	Disease Modifying Drugs
IS	Immunosuppressive
IV	Intravenous administration
JCV	John Cunningham Virus
KM	Kaplan-Meier
MS	Multiple Sclerosis
OIs	Opportunistic Infections
PML	Progressive Multifocal Leukoencephalopathy
SAE	Serious Adverse Event
SC	Subcutaneous administration
SD	Standard Deviation

2 STUDY INFORMATION

Title	Long-term surveillance of patients with multiple sclerosis to report progressive multifocal leukoencephalopathy and other serious opportunistic infections among patients treated with natalizumab
Active substance	INN: natalizumab ATC: L04AA23
Medicinal product	Tysabri
Marketing authorisation holder	Biogen Netherlands B. V.
Research question and objectives	To estimate the incidence of progressive multifocal leukoencephalopathy and opportunistic infections among all patients taking natalizumab
Country of study	Czech Republic
Source	ReMuS, Czech Republic MS Registry, Endowment Fund IMPULS

2.1. Context and project description

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system that affects approximately 2.8 million people worldwide. Natalizumab (Tysabri®) is a therapeutic humanized monoclonal antibody used for the treatment of multiple sclerosis.

Project Topik is a prospective observational study based on secondary use of data from the ReMuS registry, where the data on multiple sclerosis are collected. This project includes patients with multiple sclerosis who are newly treated with natalizumab from the 1st of January 2019. Patients also remain in the project if natalizumab treatment is discontinued.

This project was proposed to establish the safety profile of natalizumab and address specific safety concerns in a routine clinical practice in the Czech Republic by monitoring all serious adverse events (SAEs), particularly progressive multifocal leukoencephalopathy (PML) and other serious opportunistic infections (OIs).

2.2. Variables

The following table describes all analysed variables, which are divided into five groups: demographic parameters, treatment parameters, laboratory tests, pregnancy, and adverse events (AE).

Table 1 Classes of analysed variables

Variable	Categorical variable	Continuous variable
Demographic parameters		
Sex	X	
Health insurance company	X	
Region of residence	X	
Age at last visit		X
Age at the time of disease onset		X
Duration of MS		X
Treatment parameters		
Natalizumab treatment duration		X
Reason for discontinuation	X	
Previous DMD	X	
Duration of previous DMD		X
IS therapy	X	
Duration of IS therapy		X
Route of administration	X	
Laboratory tests		
JCV antibody formation	X	
JCV index		X
Neutralising antibody formation	X	
Pregnancy		
Pregnancy	X	
Breastfeeding	X	X
Adverse events		
PML	X	X
OI	X	X
SAE	X	X
Malignancy	X	
Hypersensitivity reaction	X	

2.3. Statistical analysis

All collected parameters were analysed using descriptive statistics. The categorical variables are presented as the number of patients in the groups and the percentage of the total number of analysed patients or the number of patients with a valid value, if appropriate. Continuous variables are described by the number of patients with a valid value, mean, standard deviation (SD), median, minimum, and maximum.

Where event number allowed, Kaplan Meier (KM) curves with 95% confidence intervals (CI) had been calculated for time-to-event endpoint (PML diagnosis following initiation of natalizumab treatment). KM curves are presented for each prior DMD (disease modifying drugs) treatment among anti-JCV (John Cunningham Virus) antibody positive patients, with and without prior immunosuppressant exposure.

Where event number allowed, also the PML hazard ratio were determined for each prior DMD among anti-JCV antibody positive patients and for patients with and without prior IS exposure. Additionally, incidence and incidence rate (per 1000 persons/year) of other serious OIs were determined.

Since 2021, a new form of natalizumab administration has been approved. Therefore, in addition to the current intravenous (IV) form, the subcutaneous (SC) form has also been added to the ReMuS registry. For selected analyses, patients were divided into groups according to the recorded forms of administration: 1. only IV; 2. only SC; 3. first IV, then SC; 4. first SC, then IV; 5. first IV, then SC and then IV; 6. first SC, then IV and then SC; 7. first IV, then SC, then IV, and then SC; 8. first SC, then IV, then SC, and then IV. Only groups with more than one patient are listed in the tables and figures.

3 RESULTS

This analysis evaluated the period from the 1st of January 2019 to the 31st of December 2024. Only patients with informed consent and with available data on the natalizumab treatment were included in the analysis.

At the end of 2024, a total of 675 patients were included in project Topik. Almost 70% of patients had the last form of administration as SC, while 30% of patients had the IV form of administration (Table 2). At the end of 2024, a total of 506 patients (75.0%) were still being treated with natalizumab, 169 patients (25.0%) had stopped natalizumab treatment and had not restarted by the end of the year (see part 3.2.1).

In the individual years analysed, 127 (18.8%), 121 (17.9%), 149 (22.1%), 121 (17.9%), 71 (10.5%) and 86 (12.7%) patients started natalizumab treatment (Figure 1).

Table 2 Number of patients included in project Topik to the 31st of December 2024

Final safety report	Number of patients	Percentage[1)]
Total number of patients	**675**	**100.0%**
Last route of administration - IV	204	30.2%
Last route of administration - SC	471	69.8%
Still treated patients, as of 31st of December 2024	**506**	**75.0%**

[1)] Percentage is calculated from all patients included in this project (n=675). When divided by route of administration, the percentage is calculated from the total number of patients.

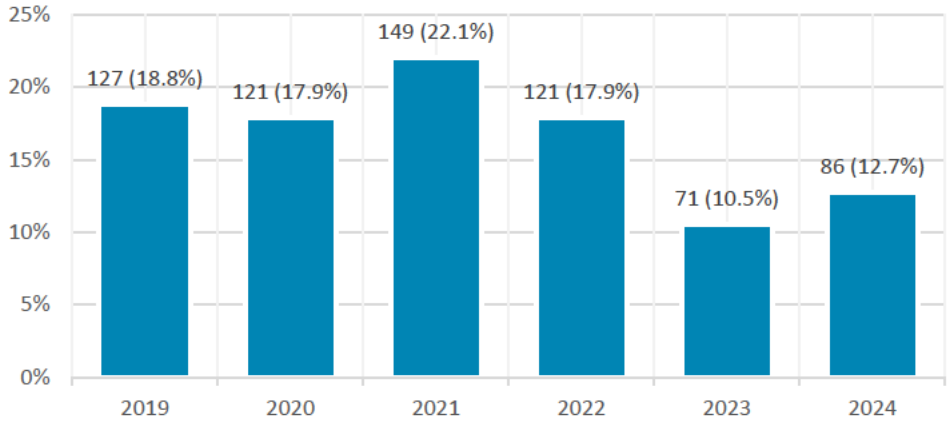

Figure 1 Number of patients stratified by treatment initiation

Figure 2 shows the numbers of patients stratified by recorded forms of natalizumab administration. A total of 184 patients (27.3%) had only the IV form of administration, 268 patients (39.7%) had the IV and then SC form of administration, and 201 patients (29.8%) had only the SC form of administration.

Some patients (2.4%) who switched from IV to SC then switched back to the IV form and some patients (0.3%) then switched back to the SC form. Similarly, some patients (0.6%) with the SC form then switched to the IV form.

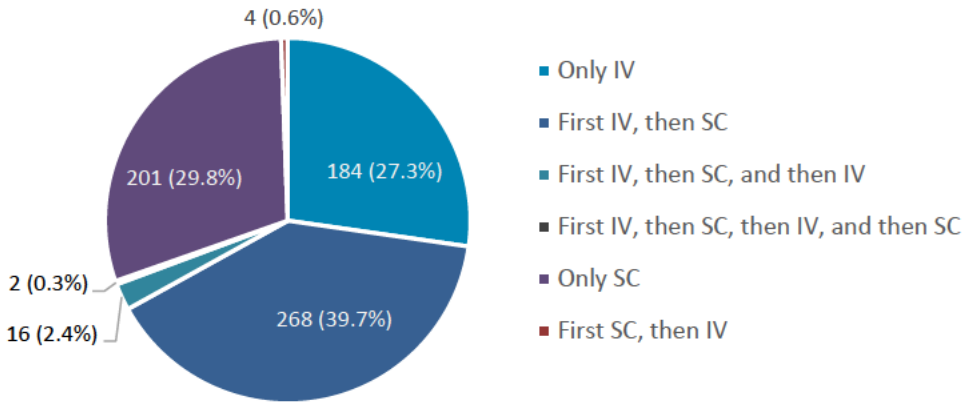

Figure 2 Number of patients stratified by recorded routes of administration

3.1. Patients' demographic and clinic characteristics

The data in this chapter are as of 31st of December 2024. Figure 3 shows the proportion of female patients in project Topik, a total of 77.8% of the patients analysed were women.

Table 3 presents the health insurance company code. More than half of the patients (56.0%) were insured with the [redacted] The second most represented insurance company was [redacted] and the third most represented insurance company was [redacted].

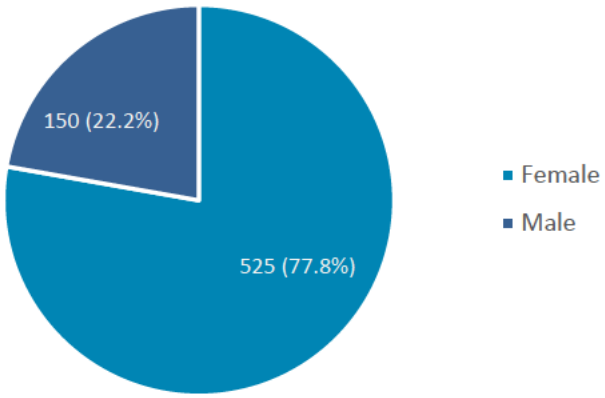

Figure 3 Sex

Table 3 Health insurance company code

Health insurance company code	Number of patients	Percentage
[redacted]	378	56.0%
[redacted]	47	7.0%
[redacted]	80	11.9%
[redacted]	57	8.4%
[redacted]	8	1.2%
[redacted]	85	12.6%
[redacted]	20	3.0%

As shown in Table 4, patients from all regions of the Czech Republic and two patients from abroad were included in the analysis.

Table 4 Region of residence

Region of residence	Number of patients	Percentage
Jihočeský	46	6.8%
Jihomoravský	74	11.0%
Karlovarský	9	1.3%
Královéhradecký	22	3.3%
Liberecký	14	2.1%
Moravskoslezský	63	9.3%
Olomoucký	41	6.1%
Pardubický	57	8.4%
Plzeňský	48	7.1%
Praha	96	14.2%
Středočeský	96	14.2%
Ústecký	42	6.2%
Vysočina	28	4.1%
Zlínský	37	5.5%
Foreign	2	0.3%

Table 5 shows age and duration from the disease onset. The mean age at last recorded visit in ReMuS registry was 39.9 years, however, ranges from 13.8 years to 72.5 years. The mean patient age at the time of disease onset was 29.2 years. The mean duration from the date of disease onset to the data lock point (DLP) on the 31st of December 2024 was 11.0 years and median duration was 8.8 years.

Table 5 Age and duration

Age and duration	Number of patients	Mean	SD	Median	Min	Max
Age at last visit	675	39.9	10.8	39.4	13.8	72.5
Age at the time of disease onset	675	29.2	9.4	27.5	10.3	66.9
Duration from date of onset	675	11.0	7.4	8.8	0.7	42.5

3.2. Treatment

3.2.1. Natalizumab treatment

The duration of natalizumab treatment was calculated as the time from the start of the treatment to the end of the treatment or to the data lock point in case the treatment was not discontinued by that time, regardless of any temporary discontinuation of treatment. The change between IV and SC form of administration was not considered as discontinuation of treatment. Thus, the duration of treatment was calculated regardless of the form of administration.

The mean duration of natalizumab treatment was 32.8 months (i.e., 2.7 years) for all analysed patients and 36.4 months (i.e., 3.0 years) for currently treated patients (i.e., patients still being treated at the end of 2024).

A total of 169 patients (25.0%) had natalizumab treatment discontinued, i.e., no restart of treatment was recorded by the end of 2024. The average treatment duration for these patients was 22.2 months (i.e., 1.9 years) (Table 6). Reasons of discontinuation are shown in Figure 4.

Of all currently treated patients, there were 23 patients (4.5% or 3.4% of all patients) who temporarily discontinued the natalizumab treatment for more than 3 months, 2 of them temporarily discontinued treatment twice. In case only these patients are considered, the mean duration of natalizumab treatment was 50.8 months (i.e., 4.2 years). This is the total duration of treatment including discontinuation, which averaged 8.3 months (Table 6). At the time of data export, these patients were treated again except for one patient. Reasons for temporary discontinuation were confirmed pregnancy (60.0%), patient choice (20.0%), scheduled stop (8.0%), lack of tolerance (4.0%), lack of efficacy (4.0%), and planned pregnancy (4.0%).

Table 6 Duration of natalizumab treatment for all analysed patients, for currently treated patients, for patients who discontinued the treatment, and for temporarily discontinued patients

Duration of natalizumab treatment [months]	Number of patients	Mean	SD	Median	Min	Max
All patients	675	32.8	19.9	33.3	0.0	71.8
Currently treated patients	506	36.4	19.9	37.1	0.4	71.8
Treatment discontinued	169	22.2	15.9	20.7	0.0	68.8
Temporary discontinuation[1)]						
Temporarily discontinued patients	23	50.8	13.7	52.9	26.5	71.8
Duration of temporary discontinuation	25	8.3	4.8	6.5	3.4	17.5

[1)] In total, 23 patients temporarily discontinued the treatment, 2 of them twice. At the time of data export, these patients were treated again except for one patient.

As the Figure 4 shows, the most frequent reasons for discontinuation of the treatment were JCV positivity (30.8%), lack of tolerance (14.2%), adverse event (10.7%), allergic reaction (8.9%), persistence of relapses (8.3%), progression of disease (8.3%), and lack of efficacy (6.5%). Other reasons for discontinuation that occurred in less than 10 patients were patient choice/convenience, lost to follow-up, persisting MRI activity, pregnancy confirmed, pregnancy planning, scheduled stop/temporary discontinuation, non-adherence and progression of EDSS.

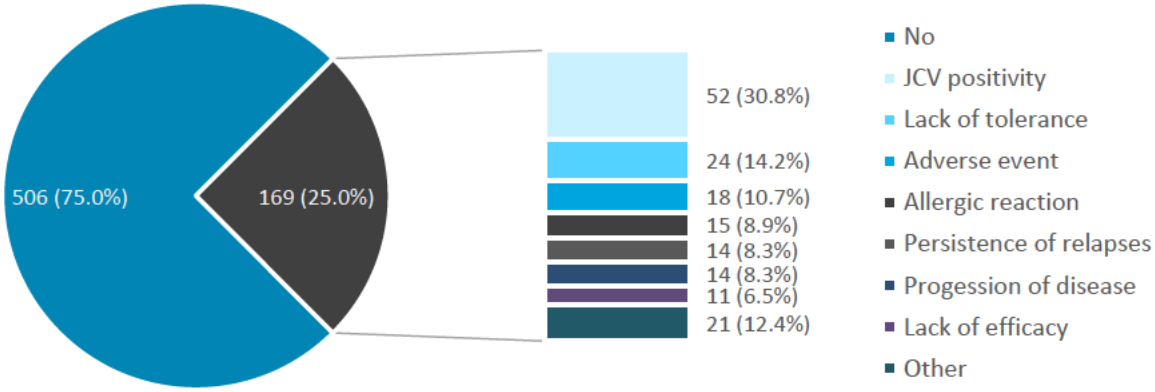

Figure 4. Discontinuation of natalizumab treatment and reasons for discontinuation

3.2.2. Previous DMD treatment

The following Table 7 shows active substances of previous DMD treatment. The most used drugs were fingolimod (16.4%), glatiramer acetate (15.7%), interferon beta-1a (13.9%), and dimethyl fumarate (13.5%). A total of 107 patients (15.9%) did not receive any DMD treatment and natalizumab was their first DMD treatment.

As the Table 8 shows, the mean duration of previous DMD treatment was 2.3 years with a median value of 1.3 years.

Table 7 Active substances of previous DMD treatment

Previous DMD treatment	Number of patients	Percentage
alemtuzumab	1	0.1%
cladribine	27	4.0%
dimethyl fumarate	91	13.5%
fingolimod	111	16.4%
glatiramer acetate	106	15.7%
interferon beta-1a	94	13.9%
interferon beta-1b	11	1.6%
ocrelizumab	22	3.3%
ofatumumab	18	2.7%
peginterferon beta-1a	34	5.0%
ponesimod	2	0.3%
rituximab	0	0.0%
siponimod	1	0.1%
teriflunomide	44	6.5%
Study medication	6	0.9%
Not treated with DMD	107	15.9%

Table 8 Duration of previous DMD treatment

Duration of previous DMD treatment [years]	Number of patients	Mean	SD	Median	Min	Max
Duration of previous DMD treatment	568	2.3	2.8	1.3	0.0	19.4

3.2.3. Immunosuppressive therapy

Immunosuppressive (IS) therapy was analysed at any time in the past independently of the natalizumab treatment. From all IS drugs, the following active substances were selected for the analysis: azathioprine, cyclophosphamide, cyclosporine, methotrexate, mitoxantrone and mycophenolate mofetil. When interpreting these data, it should be taken into consideration that the number of reported IS drugs is the total number including use of multiple drugs per patient.

A total of 23 patients (3.4%) received IS therapy, three of them twice and two patients received IS therapy three times. Thus, a total of 30 treatments were recorded. A total of 19 patients (63.3%) received an active substance azathioprine, 8 patients (26.7%) received cyclophosphamide, 2 patients (6.7%) received an active substance

mitoxantrone, and one patient (3.3%) received methotrexate (Figure 5). The mean duration of IS therapy was 2.2 years, but it should be bear in mind that total number of treatments is not representative. In addition, the mean time from the end of IS therapy to the start of natalizumab treatment was 11.5 years (Table 9).

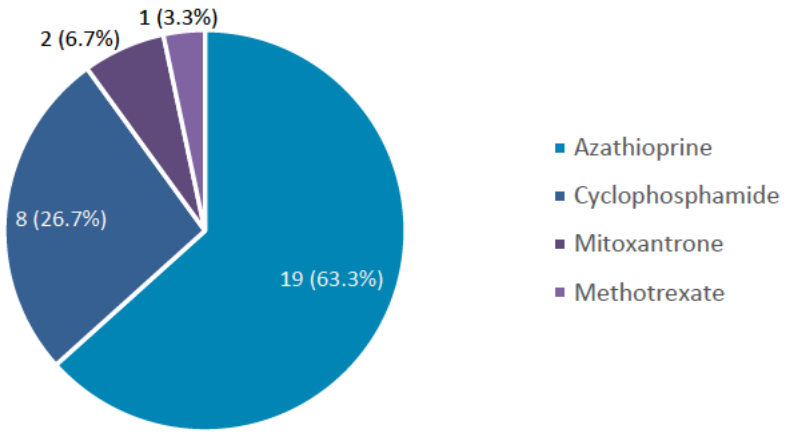

Figure 5 Immunosuppressive therapy

Table 9 Duration of immunosuppressive therapy

Duration of IS therapy [years]	Number of patients	Mean	SD	Median	Min	Max
Duration of IS therapy	30	2.2	2.9	0.5	0.0	8.5
Duration from IS therapy to natalizumab treatment	30	11.5	5.7	12.2	0.0	22.8

3.3. Antibody formation

Regarding antibody formation, JCV and neutralising anti-natalizumab antibodies were analysed.

3.3.1. JCV

JCV was analysed at the time of natalizumab treatment initiation and at the time of the last examination before the DLP.

Natalizumab treatment initiation

At the time of natalizumab initiation, 131 patients (19.4%) were JCV positive, and 540 patients (80.0%) were JCV negative. Four patients (0.6%) had missing information at the time of treatment initiation (Figure 6). The mean value of JCV index was 0.9 units with a median value of 0.6 units (Table 10).

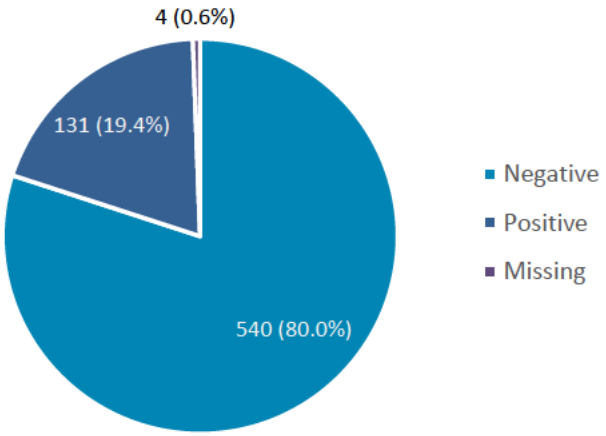

Figure 6 JCV antibody formation at the time of natalizumab initiation

Table 10 JCV antibody index at the time of natalizumab initiation in patients with positive JCV antibody formation

JCV antibody index	Number of patients	Mean	SD	Median	Min	Max
JCV positive	131	0.9	0.8	0.6	0.0	3.8

Table 11 below shows the distribution of JCV positive patients according to active substances of their previous DMD treatment. Only DMDs that were recorded in at least one patient are included in the table.

Table 11 Active substances of previous DMD treatment in patients with positive JCV antibody formation at the time of natalizumab initiation

Previous DMD treatment	Number of patients	Percentage[1)]
cladribine	4	3.1%
dimethyl fumarate	17	13.0%
fingolimod	29	22.1%
glatiramer acetate	17	13.0%
interferon beta-1a	15	11.5%
interferon beta-1b	3	2.3%
ocrelizumab	4	3.1%
ofatumumab	6	4.6%
peginterferon beta-1a	5	3.8%
ponesimod	1	0.8%
siponimod	1	0.8%
teriflunomide	9	6.9%
Study medication	1	0.8%
Not treated with DMD	19	14.5%

[1)] Percentage is calculated from patients with positive JCV antibody formation at the time of natalizumab initiation (n=131).

The last available examination

From the total amount of 675 patients, 188 patients (27.9%) were JCV positive, and 487 patients (72.1%) were JCV negative at the last examination before the DLP. The figure below shows the distribution of patients according to the recorded forms of administration (Figure 7).

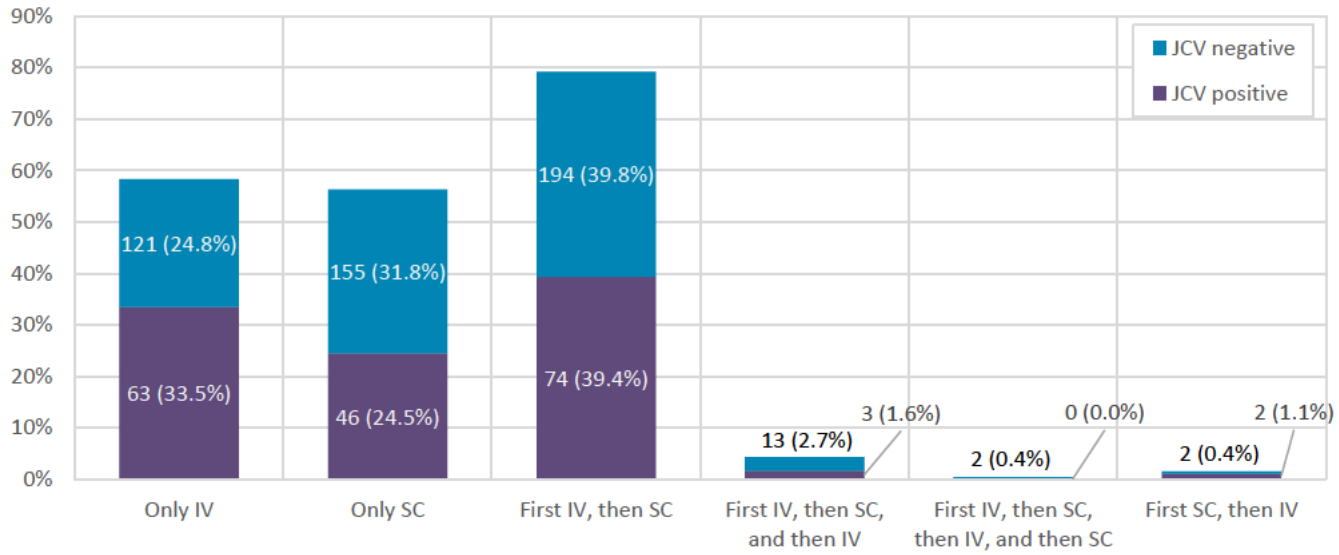

Figure 7 JCV antibody formation at the last examination, divided by routes of administration

JCV index was analysed among anti-JCV antibody positive patients. The mean value of JCV index was 1.2 units with a median value of 0.8 units. The value ranged from 0.2 units to 4.6 units (Table 12).

Table 12 JCV antibody index at the last examination in patients with positive JCV antibody formation, divided by routes of administration

JCV antibody index	Number of patients	Mean	SD	Median	Min	Max
JCV index	**188**	**1.2**	**1.1**	**0.8**	**0.2**	**4.6**
Only IV	63	1.5	1.1	1.2	0.2	3.9
Only SC	46	1.1	1.1	0.6	0.2	4.6
First IV, then SC	74	1.0	1.0	0.6	0.2	4.4
First IV, then SC, and then IV	2	1.9	2.0	1.9	0.5	3.3
First SC, then IV	3	1.7	1.5	1.3	0.4	3.4

When stratified by JCV antibody index value, a total of 102 patients (54.3%) had a JCV value less or equal to 0.9, 34 patients (18.1%) had a JCV value between 0.9 and 1.5, and the remaining 52 patients (27.7%) had a value greater than 1.5 at the last examination before DLP (Table 13).

Table 13 JCV antibody index at the last examination in patients with positive JCV antibody formation, divided categorically

JCV antibody formation divided categorically	Number of patients	Percentage[1)]
JCV positive	**188**	**100.0%**
Less than or equal to 0.9	102	54.3%
Between 0.9 - 1.5	34	18.1%
Larger or equal to 1.5	52	27.7%

[1)] Percentage is calculated from patients with positive JCV antibody formation at the last examination (n=188).

Of the 188 JCV positive patients, a total of 88 (46.8% or 13.0% of all patients) were still on natalizumab treatment at the end of 2024. A total of 71 patients (80.7%) had a JCV value less or equal to 0.9, 13 patients (14.8%) had a JCV

value between 0.9 and 1.5, and the remaining 4 patients (4.5%) had a value greater than 1.5 at the last examination before DLP (Table 14).

Table 14 JCV antibody index at the last examination in still treated patients (as od 31st December 2024) with positive JCV antibody formation, divided categorically

JCV antibody formation divided categorically	Number of patients	Percentage[1)]
Still treated JCV positive	**88**	**100.0%**
Less than or equal to 0.9	71	80.7%
Between 0.9 - 1.5	13	14.8%
Larger or equal to 1.5	4	4.5%

[1)] Percentage is calculated from still treated patients with positive JCV antibody formation at the last examination (n=88).

Figure 8 below shows the JCV positive antibody formation at the last examination and natalizumab treatment at the end of 2024.

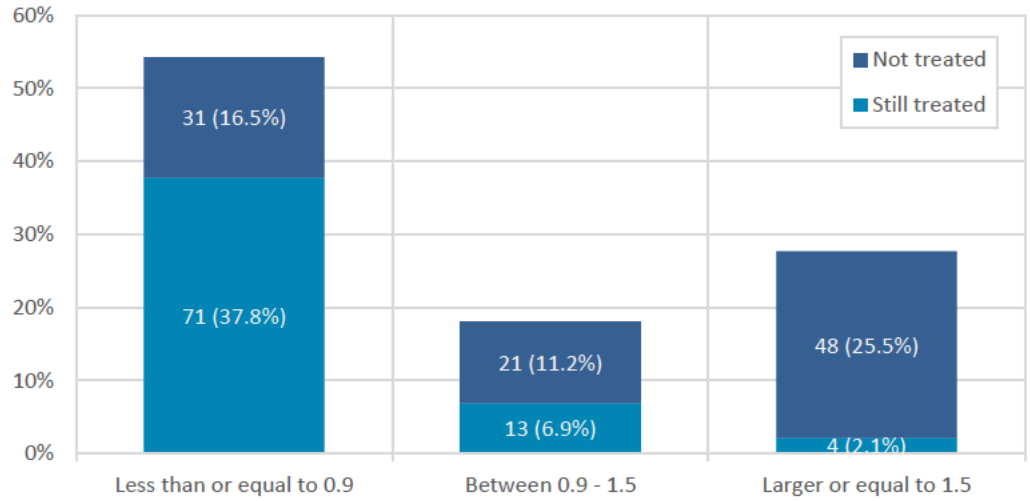

Figure 8 JCV antibody formation at the last examination, stratified by natalizumab treatment as of 31st December 2024

Table 15 below shows the distribution of JCV positive patients according to active substances of their previous DMD treatment. Only DMDs that were recorded in at least one patient are included in the table.

Table 15 Active substances of previous DMD treatment in patients with positive JCV antibody formation at the last examination

Previous DMD treatment	Number of patients	Percentage[1)]
cladribine	5	2.7%
dimethyl fumarate	24	12.8%
fingolimod	33	17.6%
glatiramer acetate	28	14.9%
interferon beta-1a	28	14.9%
interferon beta-1b	3	1.6%
ocrelizumab	7	3.7%
ofatumumab	5	2.7%
peginterferon beta-1a	9	4.8%

ponesimod	1	0.5%
siponimod	1	0.5%
teriflunomide	10	5.3%
Study medication	2	1.1%
Not treated with DMD	32	17.0%

[1)] Percentage is calculated from patients with positive JCV antibody formation at the last examination (n=188).

3.3.2. Neutralising antibody formation

The formation of neutralizing anti-natalizumab antibodies was evaluated at the last available examination in a total of 203 patients (30.1%). A total of 195 patients (96.1% or 28.9% of all patients) were tested negative and 7 patients positive (3.4% or 1.0% of all patients). One patient (0.5% or 0.1% of all patients) had unstable sample. Table 16 shows the distribution of patients according to the recorded forms of administration.

Table 16 Neutralising antibody formation during natalizumab treatment, divided by routes of administration

Neutralising antibody formation	Number of patients	Percentage[1)]
Positive	**7**	**1,0%**
Only IV	1	14,3%
Only SC	5	71,4%
First IV, then SC	1	14,3%
Negative	**195**	**28,9%**
Only IV	25	12,8%
Only SC	91	46,7%
First IV, then SC	71	36,4%
First IV, then SC, and then IV	6	3,1%
First SC, then IV	2	1,0%
Unstable sample	**1**	**0,1%**
Only SC	1	100,0%
Missing	**473**	**69,9%**

[1)] Percentage is calculated from all patients included in this project (n=675). When divided by route of administration, the percentage is calculated from the parent category.

Table 17 below shows the distribution of patients with positive neutralising antibody formation according to active substances of their previous DMD treatment. Only DMDs that were recorded in at least one patient are included in the table. When interpreting these data, it should be taken into consideration that the number of patients is not representative.

Table 17 Active substances of previous DMD treatment in patients with positive neutralising antibody formation

Previous DMD treatment	Number of patients	Percentage[1)]
dimethyl fumarate	2	28.6%
glatiramer acetate	1	14.3%
interferon beta-1a	1	14.3%
Not treated with DMD	3	42.9%

[1)] Percentage is calculated from patients with positive neutralising antibody formation (n=7).

3.4. Pregnancy and breastfeeding

Pregnancy and breastfeeding were analysed during the natalizumab treatment, i.e., any overlap of pregnancy and breastfeeding with natalizumab treatment was analysed.

Of the 525 female patients, 57 patients (10.9%) delivered babies during the natalizumab treatment, and 8 patients (1.5%) had miscarriages during the treatment. A total of 13 patients (2.5%) who had been pregnant during the natalizumab treatment were still pregnant at the time of DLP (Table 18).

Table 18 Pregnancy in female patients

Pregnancy	Number of patients	Percentage[1)]
Delivery	57	10.9%
Termination/Miscarriage	8	1.5%
Ongoing	13	2.5%

[1)] Percentage is calculated from female patients included in this project (n=525).

Breastfeeding during the natalizumab treatment was recorded in a total of 33 female patients (6.3%) and the mean duration of breastfeeding was 320.5 days (10.5 months) (Table 19).

Table 19 Duration of breastfeeding in female patients

Duration of breastfeeding [days]	Number of patients	Mean	SD	Median	Min	Max
Duration of breastfeeding	33	320.5	306.1	193.0	6.0	1130.0

3.5. Serious adverse events

Serious adverse event (SAE) means such adverse event (AE) that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in permanent or significant damage to health or limitation of capabilities or is manifested as a congenital anomaly or birth defect in offspring, irrespective of the administered dose of the medicinal product.

The following conditions are considered as hypersensitivity reactions: allergy, anaphylaxis, and injection reaction.

SAEs were analysed in all 675 patients and were analysed throughout the entire follow-up period, i.e., regardless of whether natalizumab treatment was still ongoing or not.

Since the 1st of January 2019 there have been a total of 46 SAEs. In 1 patient (0.1%) it was opportunistic infection (only SC form), 2 patients (0.3%) had hypersensitivity reaction (both with only IV form), 4 patients (0.6%) had malignancy (three of them with only IV form, one had IV and then SC form) and 39 patients (5.8%) had other SAE (eleven of them with only IV, seven with only SC, eighteen with IV and SC form and three with IV, SC and IV form) (Table 20).

Of the 46 reported SAEs, 36 (78.3%) occurred in patients during natalizumab treatment (at the latest on the day of treatment discontinuation), while the remaining 10 (21.7%) SAEs were reported in patients after natalizumab treatment discontinuation.

Table 20 Serious adverse events divided by routes of administration

Serious adverse events	All patients		SAE during treatment[2)]	SAE after treatment
	Number	Percentage[1)]	Number	Number
PML	**0**	**0.0%**	-	-
Other OIs	**1**	**0.1%**	**1**	-
Only SC	1	100.0%	1	-
Hypersensitivity reactions	**2**	**0.3%**	**2**	-
Only IV	2	100.0%	2	-
Malignancies	**4**	**0.6%**	**2**	**2**
Only IV	3	75.0%	1	2
First IV, then SC	1	25.0%	1	-
Other serious adverse events	**39**	**5.8%**	**31**	**8**
Only IV	11	28.2%	6	5
Only SC	7	17.9%	6	1
First IV, then SC	18	46.2%	17	1
First IV, then SC, and then IV	3	7.7%	2	1
Total	**46**	**6.8%**	**36**	**10**

[1)] Percentage is calculated from all patients included in this project (n=675). When divided by route of administration, the percentage is calculated from the number of SAE.

[2)] During natalizumab treatment, i.e., at the latest on the day of treatment discontinuation.

3.5.1. Kaplan-Meier estimate

Since there was no recorded PML, KM curves cannot be plotted.

3.5.2. Hazard ratio

Since there was no recorded PML, PML hazard ratio cannot be calculated.

3.5.3. Incidence and incidence rate

One serious OI has been recorded, previous DMD was peginterferon beta-1a (Plegridy).

The incidence was calculated for all 675 patients included in this project to the 31st of December 2024. The incidence of other serious OIs in analysed population was 1.48 per 1000 patients/year. The incidence rate (or incidence density) for analysed population was 0.54 per 1000 patients-years.

4 CONCLUSION

The final comparative safety report to the 31st of December 2024 was performed. The aim was to characterize the safety profile of natalizumab in a routine clinical practice in the Czech Republic by monitoring SAEs.

This analysis evaluated the period from the 1st of January 2019 to the 31st of December 2024. At the end of 2024, a total of 675 patients were included in project Topik, of whom 506 (75.0%) were still on natalizumab. In total, 27.3% of patients had only the IV form of administration, 39.7% of patients had the IV and then SC form of administration, and 29.8% of patients had only the SC form of administration. Some patients (3.3%) had other routes of administration.

Of the patients analysed, 77.8% were women. The mean age at last visit was 39.9 years and the mean patient age at the time of disease onset was 29.2 years. The mean duration from the date of disease onset to the 31st of December 2024 was 11.0 years. More than half of the patients (56.0%) were insured with [redacted]. Patients from all regions of the Czech Republic and two patients from abroad were included in the analysis.

The mean duration of natalizumab treatment was 2.7 years for all analysed patients and 3.0 years for currently treated patients. Of all currently treated patients, 4.5% had temporarily discontinued the natalizumab treatment during follow-up and were back on treatment at the end of 2024, except for one patient. The mean duration of treatment discontinuation was 8.3 months.

A total of 25.0% of patients permanently discontinued natalizumab treatment, with the mean duration of 1.9 years. The most frequent reasons for discontinuation of the treatment were JCV positivity (30.8%), lack of tolerance (14.2%), adverse event (10.7%), allergic reaction (8.9%), persistence of relapses (8.3%), progression of disease (8.3%), and lack of efficacy (6.5%).

The most frequent active substances in previous DMD treatments were fingolimod (16.4%), glatiramer acetate (15.7%), interferon beta-1a (13.9%), and dimethyl fumarate (13.5%). The mean duration of previous DMD treatment was 2.3 years. A total of 15.9% of patients had received no treatment for DMD and natalizumab was their first treatment for DMD.

At the time of natalizumab initiation, 19.4% of patients were JCV positive, and 80.0% of patients were negative. The mean value in JCV positive patients at the time of treatment initiation was 0.9 units.
In total, 27.9% of patients were JCV positive, and 72.1% were negative at the last examination before the DLP. The mean value in JCV positive patients was 1.2 units. When stratified by JCV antibody index value, a total of 54.3% of patients had a JCV value less or equal to 0.9, 18.1% had a JCV value between 0.9 and 1.5, and the remaining 27.7% had a value greater than 1.5 at the last examination before DLP.
The formation of neutralizing anti-natalizumab antibodies was evaluated in a total of 203 (30.1%) patients, almost all of them were tested negative (96.1%) at the last examination before the DLP.

Of the 525 female patients, 10.9% delivered babies during the natalizumab treatment, and 1.5% of patients had miscarriages during the treatment. A total of 2.5% of patients who had been pregnant during the natalizumab treatment were still pregnant at the time of DLP. Breastfeeding during the natalizumab treatment was recorded in a total of 6.3% of patients and the mean duration of breastfeeding was 10.5 months.

SAEs were analysed in all 675 patients and were analysed throughout the entire follow-up period, i.e., regardless of whether natalizumab treatment was still ongoing or not. In total, 46 SAEs occurred since the 1st of January 2019. In 0.1% of patients it was opportunistic infection, 0.3% of patients had hypersensitivity reaction, 0.6% of patients had malignancy and 5.8% of patients had other SAE. Of the 46 reported SAEs, 78.3% occurred in patients during natalizumab, while the remaining 21.7% of SAEs were reported in patients after natalizumab treatment discontinuation.

Because there was no recorded PML since the 1st of January 2019, neither the PML hazard ratio nor the KM curves could be calculated. The incidence was calculated for all 675 patients included in this project to the 31st of December 2024. The incidence of other serious OIs in analysed population was 1.48 per 1000 patients/year. The incidence rate (or incidence density) for analysed population was 0.54 per 1000 patients-years.