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(54) Benævnelse: **DOSERINGSREGIME FOR PEGYLERET INTERFERON**

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# DESCRIPTION

## CROSS-REFERENCE TO RELATED APPLICATION

**[0001]** This application claims priority to European Patent Application No. 14192114.8, filed on November 6, 2014.

## BACKGROUND

**[0002]** Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to increase their anti-viral defenses.

**[0003]** IFNs belong to the large class of glycoproteins known as cytokines. Interferons are named for their ability to "interfere" with viral replication by protecting cells from virus infection. More than twenty distinct IFN genes and proteins have been identified in animals, including humans. They are typically divided among three classes: Type I IFN, Type II IFN, and Type III IFN. IFNs of all three classes are important for fighting viral infections and regulating the immune system.

**[0004]** Recombinant IFNs have been developed and are commercially available.

**[0005]** Due to their various biological activities, use of IFNs for treating a number of conditions, such as infectious diseases and cancers, has been proposed. However, use of IFNs has generally been limited by several shortcomings, including immunogenicity, which may lead to formation of neutralizing antibodies and loss of clinical response, and a short half-life, which means that frequent doses are required to maintain therapeutically effective concentrations of the protein.

**[0006]** These problems were partially solved by conjugating IFNs to polymers, such as polyethylene glycol. Several different types of IFN are now approved for use in humans, including a pegylated interferon-alpha-2b (Pegintron) and a pegylated interferon-alpha-2a (Pegasys). These pegylated drugs are injected once weekly, rather than two or three times per week, as is necessary for conventional interferon-alpha. When used with the antiviral drug ribavirin, pegylated interferon is effective for the treatment of hepatitis C.
"Study Drugs - Proud-PV Phase III Study", 2014 (Proud-PV, Phase III study in patients with polycythemia vera with ropeginterferon α-2b (AOP2014) versus hydroxyurea, http://www.proud-pv.com/study-drugs.html) and History of Changes for Study: NCT02218047", 2014 (https://clinicaltrials.gov/archive/NCT02218047/2014_08_14) are clinical studies outlines referring to the use of pegylated proline-interferon alpha 2b (AOP2014) in

patients with polycythemia vera.
The public summary of opinion on orphan designation, 2011, reports orphan designation for pegylated proline-interferon alpha-2b for the treatment of polycythemia vera (European medicines Agency, http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2011/12/WC500119793.pdf).
Pharmaessentia Corp.", 2012, reported a 40K PEG-P-IFN-alpha-2b (P1101) for treating hepatitis C (http://www3.bio.org/bioasia-profiles/pdfs/196771.pdf).
WO2010014874A2 discloses a pegylated proline-interferon alpha-2b.
WO2009023826A1 discloses the use of a pegylated proline-interferon alpha-2b for treating hepatitis B virus or hepatitis C virus infections.
Gisslinger H. et al., 2015 report ropeginterferon alfa-2b for treating patients with polycythemia vera (Blood, vol. 126, no. 15, 2015, pp. 1762-1769).

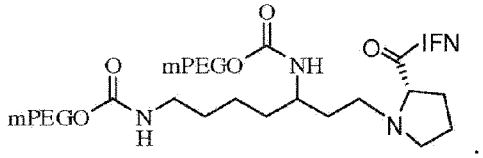
**[0007]** However, while interferon-polymer conjugates are clinically beneficial, they also have a number of adverse side effects such as flu-like symptoms, increased body temperature, feeling ill, fatigue, headache, muscle pain, convulsion, dizziness, hair thinning, and depression. Erythema, pain and hardness on the spot of injection are also frequently observed.

**[0008]** Side effects are particularly important considerations when long term treatment is needed. Reducing the frequency of administration and total cumulative amount administered may decrease side effects and increase tolerability. However, previous such attempts did not show any satisfactory therapeutic effectiveness.

**SUMMARY**

**[0009]** Herein encompassed is a pegylated type I interferon for use in the treatment of a myeloproliferative disease in a subject, wherein

the pegylated type I interferon is



;

wherein mPEG has a molecular weight of 20 kD and IFN is an interferon-$\alpha_{2b}$, and wherein a 50 to 540 µg dose of the pegylated type I interferon is administered subcutaneously to a subject in need thereof at a first regular interval of 2 weeks for a first treatment period for longer than 1 year, subsequently followed by a second treatment period at a second administration interval of every 4 weeks, wherein the myeloproliferative disease is polycythemia vera and wherein the dosage of the first and the second administration interval remains unchanged.

**[0010]** The total amount of the pegylated type I interferon administered to the subject per a given period during the second treatment period is lower than the total amount administered per the given period during the first treatment period.

**[0011]** In an embodiment, the first treatment period continues until the subject exhibits (i) normalization of at least one hematological parameter and/or (ii) at least 50% reduction of JAK2V617F allelic burden.

**[0012]** In the embodiment, the first interval is 2 weeks and the second interval is 4 weeks.

**[0013]** The details of one or more embodiments are set forth in the accompanying drawing and the description below. Other features, objects, and advantages of the embodiments will be apparent from the description and drawing, and from the claims.

## BRIEF DESCRIPTION OF DRAWINGS

**[0014]**

FIG. 1 is a bar graph showing maintenance of any hematological response before and after switch to a 4-week regimen.

FIG. 2 is a bar graph showing maintenance of any molecular response before and after switch to 4-week regimen.

## DETAILED DESCRIPTION

**[0015]** Data described below demonstrated that, surprisingly, administration of a pegylated type I interferon at long intervals can provide efficient and even increased responses in subjects compared to a weekly or biweekly administration regimen. The reduced injection frequency also clearly and significantly improved tolerability and reduced adverse events. The data further showed that continuous administration of low doses of a pegylated interferon is an important variable for inducing molecular responses. It was also shown that the effects of long term administration of a pegylated type I interferon at low doses are pleiotropic, such as induction of immune-surveillance.

**[0016]** Accordingly, described herein are methods that involve administering a pegylated type I interferon at a regular interval to treat a subject in need thereof (e.g., a subject with an infectious disease, a cancer, or a myeloproliferative disease).

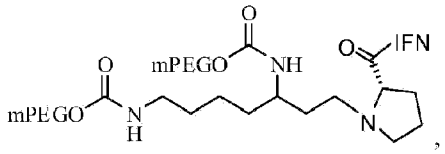
**[0017]** The pegylated type I interferon administered at a regular interval is interferon-α 2b.

**[0018]** Lyophilized formulations containing a peg-interferon-α -2b, dibasic sodium phosphate anhydrous, monobasic sodium phosphate dihydrate, sucrose and polysorbate 80 are marketed by Schering Corporation, Kenilworth, NJ as PEGIntron® vials and PEG-Intron® Redipen (See PEG-Intron® Product Information, Rev. 2/05.). The Redipen® is a dual-chamber glass cartridge containing lyophilized PEGIntron in one chamber and sterile water for injection in the other chamber. The manufacturer recommends room temperature storage for PEG-Intron® vials (i.e., 25° C), and refrigerated storage for PEG-Intron Redipen cartridges (i.e., 2° to 8° C).

**[0019]** A pegylated interferon-α-2b made of human proteins is for example available under the trade name Pegasys®.

**[0020]** In one embodiment, a mono-pegylated, proline-substituted interferon-α-2b is administered at a regular interval.

**[0021]** In one embodiment, the conjugate is AOP2014/P1101, which has the formula:




in which mPEG has a molecular weight of 20 kD and IFN is an interferon-$\alpha_{2b}$ (e.g., a human interferon-$\alpha_{2b}$).

**[0022]** The conjugate of formula I is described in detail in WO2009/023826A1. In particular, WO2009/023826A1 teaches a method of making AOP2014/P1101.

**[0023]** In any of the methods and uses described herein, the pegylated type I interferon can be administered by any means known in the art, e.g., via subcutaneous or intravenous route. The pegylated type I interferon can be formulated as an injectable formulation.

**[0024]** The term "dose" refers to the amount of a compound administered to a subject at one time.

**[0025]** The term "interval" refers to the time between administration of two consecutive doses.

**[0026]** The treatment period can be at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months. In one embodiment, the treatment period is 2, 3, or more years.

**[0027]** A dose administered during the treatment period ranges from 50 to 540 µg. The dose can be 50 µg, up to 55 µg, specifically up to 60 µg, specifically up to 65 µg , specifically up to 75 µg, specifically up to 80 µg, specifically up to 85 µg, specifically up to 90 µg, specifically up to 95 µg, specifically up to 100 µg, specifically up to 105 µg, specifically up to 110 µg, specifically up to 115 µg, specifically up to 120 µg, specifically up to 125 µg, specifically up to 130 µg, specifically up to 135 µg, specifically up to 140 µg, specifically up to 145 µg, specifically

up to 150 µg, specifically up to 155 µg, specifically up to 160 µg, specifically up to 165 µg, specifically up to 170 µg, specifically up to 175 µg, specifically up to 180 µg, specifically up to 185 µg, specifically up to 190 µg, specifically up to 195 µg, specifically up to 200 µg, specifically up to 205 µg, specifically up to 210 µg, specifically up to 215 µg, specifically up to 225 µg, specifically up to 230 µg, specifically up to 235 µg, specifically up to 240 µg, specifically up to 245 µg, specifically up to 250 µg, specifically up to 255 µg, specifically up to 260 µg, specifically up to 265 µg, specifically up to 270 µg, specifically up to 275 µg. specifically up to 280 µg, specifically up to 285 µg, specifically up to 290 µg, specifically up to 295 µg, specifically up to 300 µg, specifically up to 305 µg, specifically up to 310 µg, specifically up to 315 µg, specifically up to 320 µg, specifically up to 325 µg, specifically up to 330 µg, specifically up to 335 µg, specifically up to 340 µg, specifically up to 345 µg, specifically up to 350 µg, specifically up to 400 µg, specifically up to 450 µg, specifically up to 500 µg, or up to 540 µg.

**[0028]** In an alternative embodiment, a dose administered during the treatment period is between 50 and 500 µg, specifically between 50 and 100 µg, alternatively between 100 and 150 µg, alternatively between 150 and 200 µg, alternatively between 200 and 250 µg, alternatively between 250 and 300 µg, alternatively between 300 and 350 µg, alternatively between 350 and 400 µg, alternatively between 400 and 450 µg, alternatively between 450 and 500 µg, or between 500 and 540 µg.

**[0029]** During any treatment period, the pegylated type I interferon can be administered at a constant dose, meaning that the same dose is administered each time or only minimally different doses are administered (e.g., dose variation or deviation of less than 10%, specifically less than 5%, specifically less than 1%). For example, the interferon can be administered at a particular dose at a regular interval for a certain time and it can then be administered at a different dose (higher or lower than the first dose) at the same regular interval.

**[0030]** The subject can be a subject who has not been treated with an interferon before or a subject who had previously been administered a dose (e.g., 12.5, 15, 18.75, or 25 µg) of a type I interferon once per week or every two weeks.

**[0031]** Administration of the pegylated type I interferon at a regular interval can be used to treat polycythemia vera,.

**[0032]** A subject in need thereof can be treated with a pegylated type I interferon using one dosage regimen for a time period and then switched to a different dosage regimen.

**[0033]** More specifically, a 50 to 540 µg dose of a pegylated type I interferon is administered to a subject in need thereof at a first regular interval for a first treatment period, , and subsequently, a 50 to 540 µg dose of the pegylated type I interferon is administered to the subject at a second regular interval for a second treatment period.

**[0034]** Subjects who show a good response to a pegylated type I interferon dosage regimen can be switched to another regimen in which the interferon is administered at a lower dose or

at a longer interval or both.

**[0035]** In one embodiment, the total amount of the pegylated type I interferon administered to the subject per a given period during the second treatment period is lower (e.g., lower by 20%, 30%, 40%, 45%, 50%, or more) than the total amount administered per the same given period during the first treatment period. For example, the monthly total amount of the interferon administered during the second treatment period can be lower (e.g., 20%, 30%, 40%, 45%, 50%, or more lower) than the monthly total amount administered during the first treatment period.

**[0036]** The dose administered during the first treatment period and the dose administered during the second treatment period can be the same but at different intervals. Alternatively, the dose administered during the second treatment period can be lower than the dose administered during the first treatment period.

**[0037]** The first treatment period and the second treatment period can separately be at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months (e.g., 2, 3, or more years).

**[0038]** The first treatment period can continue until the subject shows a good response to the treatment. Whether a subject is responding well to the treatment can be determined by a practitioner skilled in the art based on art-accepted criteria.

**[0039]** In one embodiment, the subject is switched to a second treatment regimen when he or she exhibits (i) normalization of at least one hematological parameter and/or (ii) at least 50% reduction of JAK2V617F allelic burden.

**[0040]** Specifically, a further decrease of the JAK2V617F allelic burden can be achieved due to switch to the second treatment regimen wherein the treatment interval is 4 weeks. More specifically, said reduction of the JAK2V617F allelic burden can be 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or up to 99%, specifically within a treatment period of 1, 2 or more years.

**[0041]** A hematological parameter is "normalized" when its value is deemed sufficient to alleviate a disease-associated adverse event (e.g., thrombosis or anemia) or reduce the risk thereof in the subject. Hematocrit, white blood cell count, and platelet counts are exemplary hematological parameters. Hematocrit of less than 45% (without phlebotomy in the previous two months), a platelet count of less than $400 \times 10^9$/L and a white blood cell count of less than $10 \times 10^9$/L may each be considered as a normalized hematological parameter.

**[0042]** Other indications of a good response can include a normal spleen size (measured via ultrasound), absence of any thromboembolic events, and a reduction of phlebotomy requirements by at least 50%.

**[0043]** If a subject continues to show a good response under the second treatment regimen, the subject may be switched to yet another regimen that further reduces the administration

frequency or dose (or both) of the pegylated type I interferon.

**[0044]** The specific example below is to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present disclosure to its fullest extent.

**EXAMPLE 1**

**[0045]** AOP2014/P1101 is a next generation long-acting pegylated IFN-α-2b, consisting predominantly of only one isoform, as opposed to other commercially available pegylated interferons.

**Study Design**

**[0046]** A phase I/II single arm dose escalation study with cohort extension included 51 patients with PV who could be either cytoreduction therapy naive or pretreated. AOP2014/P1101 was administered subcutaneously in a dose range of 50-540 µg every two weeks. Main objectives were to define the maximum tolerated dose as well as observe the long term safety and efficacy in terms of normalization of blood parameters and molecular abnormalities.

**[0047]** The option to switch to an "once every four weeks" schedule was implemented by the amended protocol for patients who responded well to the treatment and participated in the study for longer than one year. The dose of the study drug had to remain unchanged after the switch, resulting in a decrease (by approximately half) of the overall exposure to the drug. Outcomes of this switch are presented here.

**Results**

**[0048]** Patients were dosed every two weeks based on the Phase II dosing rules (period A - median exposure duration of 34 weeks and mean monthly dose of 484 µg) prior to the switch option. 33 patients were dosed every two weeks beyond the first year (period B - median exposure duration of 12 weeks and mean monthly dose of 413 µg), and showing benefit from treatment, were assessed as eligible for switch. 28 patients were then switched to a once every four weeks schedule (period C - median exposure duration of 42 weeks and mean monthly dose of 221 µg). Nine patients were each at a dose of 100 µg or less after the switch. Baseline characteristics of the included patients are shown in Table 1.

Table 1: Baseline information

| Parameter | Value |
|---|---|
| Safety population, patients (all treated) | 51 |
| Age at study entry, years, median (min-max) | 56 (35-82) |
| Male, n (%) | 31 (61%) |
| Splenomegaly (length >12cm on sonography), patients (%) | 31 (61%) |
| Spleen length on sonography, median in cm (min-max) | 13.1 (8.0-22.0) |
| Patients with phlebotomies in 3 months prior screening, n (%) | 31 (61%) |
| Number of phlebotomies in 3 months prior screening, median (range) | 2 (1-8) |
| PV history prior entry, months, median (Q1-Q3) | 17.0 (3.6-68.8) |
| Major cardiovascular events in the med. history, patients (%) | 11 (22%) |
| HU pre-treated, patients (%) | 17 (33%) |
| Hct, %, median (min-max) | 44.8 (36.9-53.8) |
| Platelets, G/L, median (min-max) | 429 (148-1016) |
| WBC, G/L, median (min-max) | 11.1 (4.7-30.9) |
| JAK2V617F-positive | 100% |
| %V617F allelic burden, median (min-max) | 41% (2% - 100%) |
| Safety population, patients | 51 |
| Enrolled in Phase I | 25 |
| Enrolled in Phase II | 26 |
| Follow-up duration, weeks, median (min-max) | 80 (4-170) |
| Evaluable patients with treatment duration > 1 year | 30 |
| **Arms analyzed for the current comparison** | |
| **Period A, 2-weeks regimen: all** patients excluding those who discontinued before week 18 (V5) | 45 |
| **Period B, 2-weeks regimen - MAINTAINED for the purpose:** completed the one year of treatment and became eligible for switched but were not switched for certain duration. | 33 |
| **Period C, 4-weeks regimen:** all patients who were switched to 4 week schedule. | 28 |
| Note: same patient may count twice within the contributing periods if not switched immediately but remained in a 2-week schedule beyond the first year and was switched to a 4-week schedule later on. | |

**[0049]** After the switch, blood parameters were normalized and remained stable following one year of treatment and could be maintained (hematocrit, median,% - period A: 43, period B: 43, period C: 42; WBC, median, G/l - period A: 6.1, period B: 5.9, period C: 5.7; platelets, median,

G/l - period A: 246, period B: 211, period C: 204),

**[0050]** Spleen length stayed stable within the normal range following the switch in the majority of patients either (mean, in cm - period A: 11.4, period B: 8.3, period C: 10.3).

**[0051]** Complete response as best individual response could be maintained in 42% of the patients from period A, 55% from period B, and 67% from period C, while for the partial hematological responders the results were 60%, 71% and 67%, respectively. Molecular response improved continuously over time, being maintained at the best individual level in 31% of the period A patients, compared to 42% of the period B patients and 75% of the period C patients. The decrease of application frequency and total dose exposure led to a decrease of the occurrence of all drug related adverse events from 0.17/0.09 (period A) and 0.3/0.09 (period B) to 0.08/0.03 (period C) (measured as mean count of adverse events [AE] per patient week exposure).

**[0052]** The maintenance of any hematological response before and after the switch to the 4-week regime is shown in FIG. 1 and Table 2.

Table 2: Maintenance of any hematological response between three comparison arms

| 4 weeks vs. 2 weeks p (McNemar)=0.782 | | 2 weeks | | |
|---|---|---|---|---|
| | | Not maintained | Maintained | Total |
| 4 weeks | Not maintained | 3 | 6 | 9 |
| | | 10.7% | 21.4% | 32.1% |
| | Maintained | 7 | 12 | 19 |
| | | 25.0% | 42.9% | 67.9% |
| | Total | 10 | 18 | 23 |
| | | 35.7% | 64.3% | 100.0% |
| 4 weeks vs. 2 weeks-MAINT. p (McNemar)=0.564 | | 2 weeks - MAINTAINED | | |
| | | Not maintained | Maintained | Total |
| 4 weeks | Not maintained | 3 | 5 | 8 |
| | | 11.5% | 19.2% | 30.8% |
| | Maintained | 7 | 11 | 18 |
| | | 26.9% | 42.3% | 69.2% |
| | Total | 10 | 16 | 26 |
| | | 38.5% | 61.5% | 100.0% |

**[0053]** The maintenance of any molecular response before and after the switch to the 4-week regimen is shown in FIG. 2 and Table 3.

Table 3: Maintenance of any molecular response between three comparison arms

| 4 weeks vs. 2 weeks p (McNemar)=0.020 | | 2 weeks | | |
|---|---|---|---|---|
| | | Not maintained | Maintained | Total |
| 4 weeks | Not maintained | 4 | 3 | 7 |
| | | 14.3% | 10.7% | 25.0% |
| | Maintained | 12 | 9 | 21 |
| | | 42.9% | 32.1% | 75.0% |
| | Total | 16 | 12 | 28 |
| | | 57.1% | 42.9% | 100.0% |
| 4 weeks vs. 2 weeks-MAINT. p (McNemar)=0.052 | | 2 weeks - MAINTAINED | | |
| | | Not maintained | Maintained | Total |
| 4 weeks | Not maintained | 4 | 3 | 7 |
| | | 15.4% | 11.5% | 26.9% |
| | Maintained | 10 | 9 | 19 |
| | | 38.5% | 34.0% | 73.1% |
| | Total | 14 | 12 | 26 |
| | | 53.8% | 46.2% | 100.0% |

**[0054]** The data from endpoints pre-defined in the prospective study demonstrated that the feasibility of further reducing the frequency of AOP2014/P1101 administration to once every four weeks in responding patients, previously treated every two weeks. The reduced injection frequency was not associated with a lack of response, but clearly improved tolerability. Finally, the continuous reduction of the JAK2 allelic burden in the subjects indicated that duration of interferon exposure, rather than dose, is important for inducing molecular responses. The findings described above suggest that interferon-α-associated effects in PV are pleiotropic (e.g., induction of immune-surveillance), which can be continuously maintained at lower AOP2014/P1101 levels.

**EXAMPLE 2**

**[0055]** A phase I/II single arm dose escalation study with cohort extension includes at least 30 patients with essential thromobocythemia who could be either undergo cytoreduction therapy naive or pretreated. AOP2014/P1101 is administered subcutaneously in a dose range of 50-540 µg every two weeks. The maximum tolerated dose as well as the long term safety and efficacy in terms of normalization of blood parameters and molecular abnormalities are observed.

**[0056]** The option to switch to an "once every four weeks" schedule is implemented for patients who respond well to the treatment and participate in the study for longer than one year. Patients who are dosed every two weeks beyond the first year and showing benefit from treatment are assessed as eligible for switch. The patients are then switched to a once every four weeks schedule. The dose of the study drug shall remain unchanged after the switch, resulting in a decrease (by approximately half) of the overall exposure to the drug.

**OTHER EMBODIMENTS**

**[0057]** All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

**[0058]** From the above description, one skilled in the art can easily ascertain the essential characteristics of the described embodiments, and without departing from the scope thereof, can make various changes and modifications of the embodiments to adapt it to various usages and conditions.

# REFERENCES CITED IN THE DESCRIPTION

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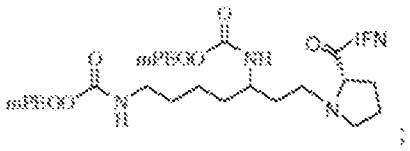
- WO2009023826A1 [0006] [0022] [0022]


**Non-patent literature cited in the description**

- **GISSLINGER H. et al.**report ropeginterferon alfa-2b for treating patients with polycythemia veraBlood, 2015, vol. 126, 151762-1769 [0006]

PATENTKRAV

1. Pegyleret type I-interferon til anvendelse ved behandling af en myeloproliferativ sygdom hos et individ, hvor
det pegylerede type I-interferon er



hvor mPEG har en molekylvægt på 20 kD, og IFN er et interferon-$\alpha_{2b}$, og hvor en 50 til 540 μg dosis af det pegylerede type I-interferon administreres subkutant til et individ med behov derfor med et første regelmæssigt interval på 2 uger i en første behandlingsperiode, som er længere end 1 år, efterfulgt af en anden behandlingsperiode med et andet administrationsinterval på hver 4. uge, hvor den myeloproliferative sygdom er polycytæmia vera, og hvor doseringen i det første og det andet administrationsinterval forbliver uændret.

2. Pegyleret type I-interferon til anvendelse ifølge krav 1, hvor den anden behandlingsperiode er mindst 2 til 12 måneder, eller behandlingsperioden er mindst 12 måneder.

3. Pegyleret type I-interferon til anvendelse ifølge krav 2, hvor den samlede mængde af det pegylerede type I-interferon, som administreres til individet i en given periode i løbet af den anden behandlingsperiode, er mindre end den samlede mængde, som administreres i den givne periode i den første behandlingsperiode.

4. Pegyleret type I-interferon til anvendelse ifølge krav 3, hvor den første behandlingsperiode fortsætter, indtil individet udviser (i) normalisering af mindst én hæmatologisk parameter og/eller (ii) mindst 50% reduktion af JAK2V617F-allelbyrde, specifikt hvor den mindst ene hæmatologiske parameter er hæmatokrit, leukocyttal (WBC - white blood cell count) eller trombocyttal.

5. Pegyleret type I-interferon til anvendelse ifølge krav 4, hvor hæmatokritten er mindre end 45%, WBC er mindre end eller lig med 10 x $10^9$/l, og trombocyttallet er mindre end eller lig med 400 x $10^9$/l.

6. Pegyleret type I-interferon til anvendelse ifølge et hvilket som helst af kravene 1-5, hvor der administreres en konstant dosis af det pegylerede type I-interferon i den første

og/eller den anden behandlingsperiode, specifikt hvor der administreres den samme konstante dosis i den første behandlingsperiode og den anden behandlingsperiode, eller den konstante dosis, som administreres i den anden behandlingsperiode, er lavere end den konstante dosis, som administreres i den første behandlingsperiode.

# DRAWINGS

FIG. 1

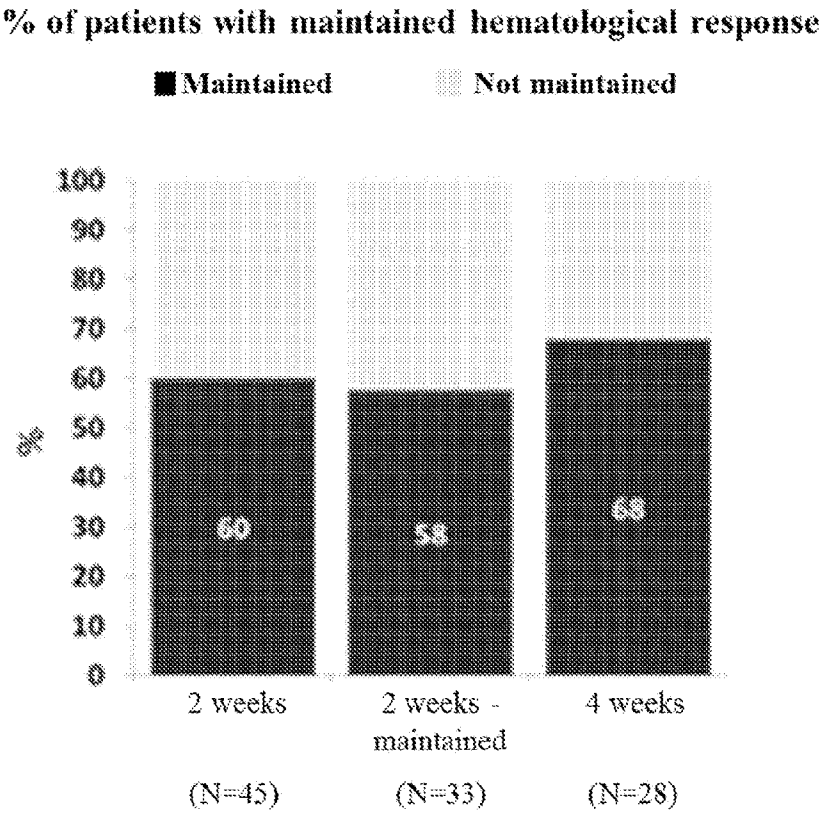
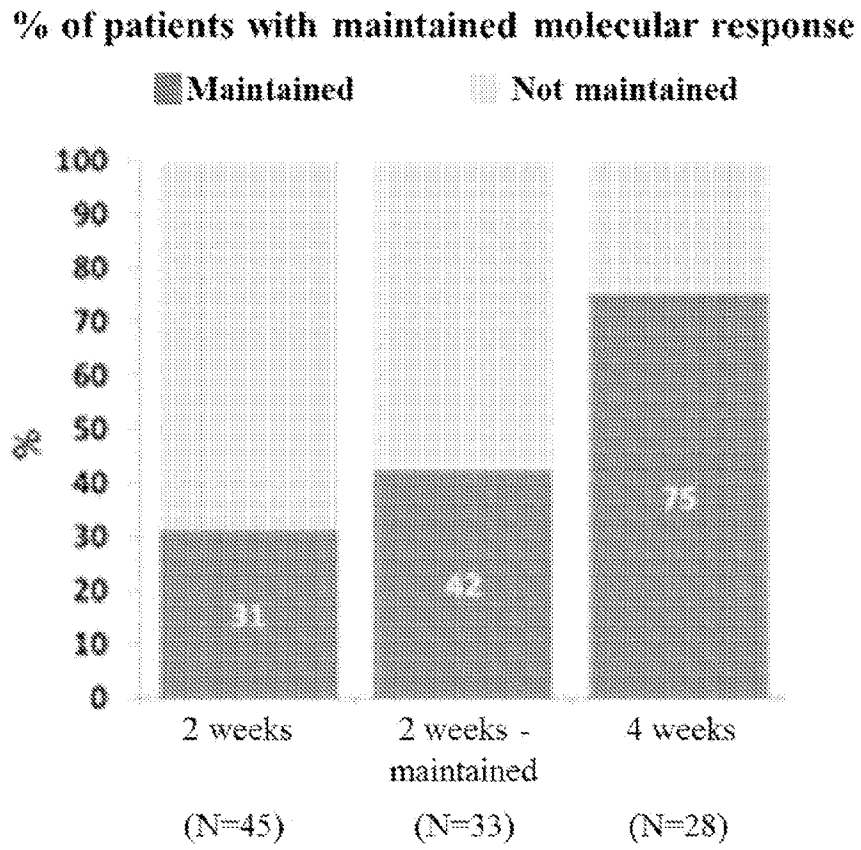


FIG. 2


% of patients with maintained molecular response
Maintained
Not maintained
100
90
80
70
60
50
40
30
20
10
0
%
31
42
75
2 weeks
(N=45)
2 weeks - maintained
(N=33)
4 weeks
(N=28)