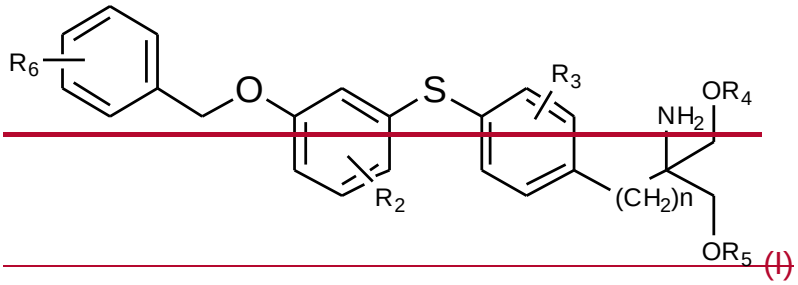
CLAIMS

1. An S1P receptor modulator, for use in treating acute myelogenous leukemia (AML) in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT).

2. The S1P receptor modulator, for use according to claim 1, wherein said S1P receptor modulator is selected among mocravimod, FTY720, siponimod, fingolimod, ozanimod, ponesimod, etrasimod, AKP-11, cenerimod, amiselimod, CBP-307, OPL-307, OPL-002, BMS-986166, SCD-044, BOS-173717, CP-1050, preferably mocravimod.

3. The S1P receptor modulator, for use according to claim 1, wherein said S1P receptor modulator is a S1P receptor agonist.

The S1P receptor modulator, for use according to claim 3, wherein the S1P receptor agonist is of the following formula (I) or (II) or (IIa) or (IIb):



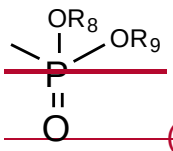
(I)

wherein

R_2 is H, halogen, trihalomethyl, C_{1-4}alkoxy, C_{1-7}alkyl, phenethyl or benzyloxy;

R_3 is H, halogen, CF_3, OH, C_{1-7}alkyl, C_{1-4}alkoxy, benzyloxy, phenyl or C_{1-4}alkoxymethyl;

each of R_4 and R_5, independently is H or a residue of formula (a)

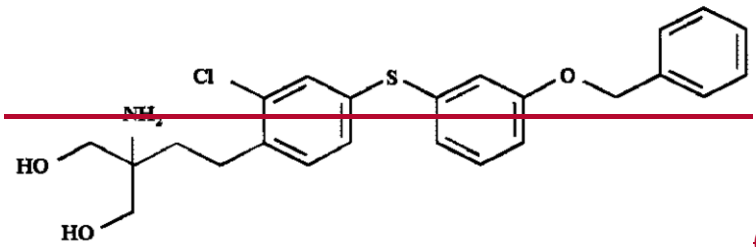


(a)

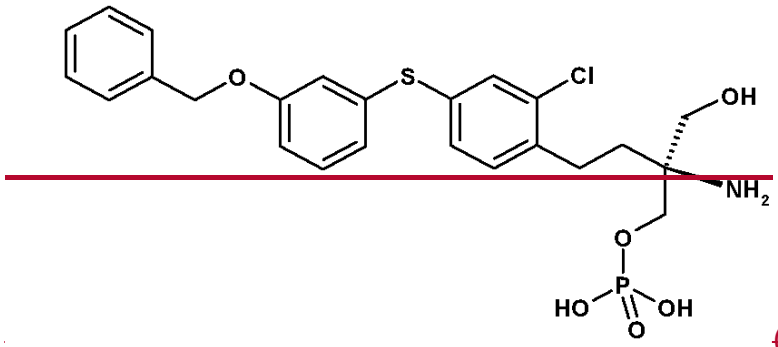
wherein each of R_8 and R_9, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

and n is an integer from 1 to 4; and

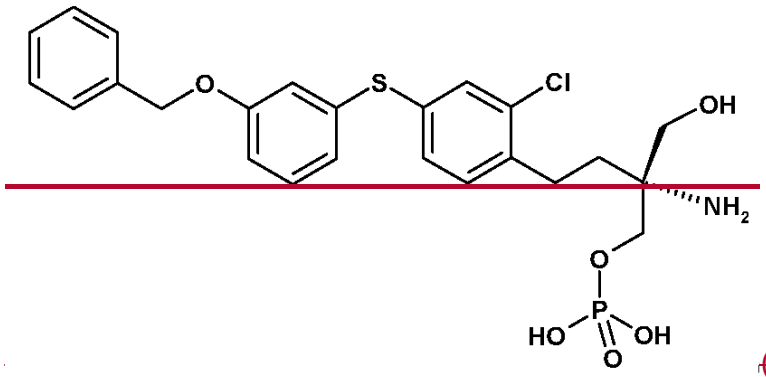
R_6 is hydrogen, halogen, C_{1-7}alkyl, C_{1-4}alkoxy or trifluoromethyl,



(II),



(IIa),



(IIb),

or pharmaceutically acceptable salts thereof.

4. The S1P receptor modulator, for use according to claim 4, wherein the S1P receptor agonist is mocravimod, or a pharmaceutically acceptable salt thereof.

4. The S1P receptor modulator for use according to any one of Claims 1-5, wherein said subject is selected among the patient population being either in first complete remission but in the adverse-risk group called “CR1 high risk”, or in second complete remission or beyond, called “CR2”, wherein said CR1 high risk, or CR2 patients are defined according to ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications of the American Society for Blood and Marrow Transplantation.

4. The S1P receptor modulator for use according to any one of claims 1-6, wherein said S1P receptor modulator is daily administered for at least 6, 7, 8, 9, 10, 11 or

12 months, or more, or until relapse, preferably from a starting day between 1-14 days prior to HSC transplant, preferably 11 days before HSC transplant.

4. The S1P receptor modulator for use according to any one of claims 1-7, wherein said S1P receptor modulator is mocravimod, and said subject is further treated with an efficient amount of immunosuppressants including at least ciclosporin A, and wherein said immunosuppressants treatment is reduced or stopped after at least 3 months, for example reduced to an amount of at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% of the starting dose after at least 3 months.

4. The S1P receptor modulator for use according to any one of claims 1-8, wherein said subject is further administered an efficient amount of an immunosuppressant essentially consisting of ciclosporin A, or of a combination of ciclosporin A and methotrexate.

4. The S1P receptor modulator for use according to claim 9, wherein said ciclosporin A is administered at a starting dose ranging between 2 to 6 mg/kg/day, preferably 3 to 5 mg/kg/day.

4. The S1P receptor modulator for use according to any one of claims 1-10, wherein said S1P receptor modulator is mocravimod, and said mocravimod is administered at a daily dose of 3mg.

4. The S1P receptor modulator for use according to any one of claims 1-10, wherein said S1P receptor modulator is mocravimod, and said mocravimod is administered at a daily dose of 1mg.

4. The S1P receptor modulator for use according to any one of claims 1-12, wherein said S1P receptor modulator is mocravimod, and said mocravimod is formulated as a solid dosage form, said solid dosage form comprising:

- mannitol, preferably at a content from 48 to 88 mg/unit, more preferably from 58 to 78mg/unit, even more preferably at a content about 68 mg/unit;

- microcrystalline cellulose, preferably at a content from 5 to 45 mg/unit, more preferably from 15 to 35 mg/unit, even more preferably at a content about 25 mg/unit;
- sodium starch glycolate, preferably at a content from 1 to 8 mg/unit, more preferably from 2 to 6 mg/unit, even more preferably at a content about 4 mg/unit;
- magnesium stearate, preferably at a content from 0.025 to 4 mg/unit, more preferably from 0.5 to 2 mg/unit, even more preferably at a content about 1 mg/unit; and
- colloidal silicon dioxide, preferably at a content from 0.125 to 2 mg/unit, more preferably from 0.25 to 1 mg/unit, even more preferably at a content about 0.5 mg/unit.

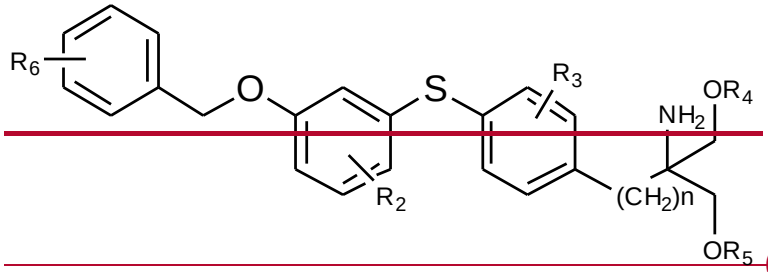
4. An S1P receptor modulator, for use according to any one of claims 1-13, wherein said S1P receptor modulator is administered in an amount sufficient for treating chronic GVHD, typically for delaying chronic GVHD onset.

4. An S1P receptor modulator, for use in treating chronic GVHD in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT), typically for delaying chronic GVHD onset.

4. The S1P receptor modulator, for use according to claim 15, wherein said S1P receptor modulator is selected among mocravimod, FTY720, siponimod, fingolimod, ozanimod, ponesimod, etrasimod, AKP-11, cenerimod, amiselimod, CBP-307, OPL-307, OPL-002, BMS-986166, SCD-044, BOS-173717, CP-1050, preferably mocravimod.

4. The S1P receptor modulator, for use according to claim 15, wherein said S1P receptor modulator is a S1P receptor agonist.

4. The S1P receptor modulator, for use according to claim 17, wherein the S1P receptor agonist is of the following formula (I) or (II) or (IIa) or (IIb) :



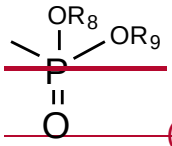
(I)

wherein

R_2 is H, halogen, trihalomethyl, C_{1-4}alkoxy, C_{1-7}alkyl, phenethyl or benzyloxy;

R_3 is H, halogen, CF_3, OH, C_{1-7}alkyl, C_{1-4}alkoxy, benzyloxy, phenyl or C_{1-4}alkoxymethyl;

each of R_4 and R_5, independently is H or a residue of formula (a)

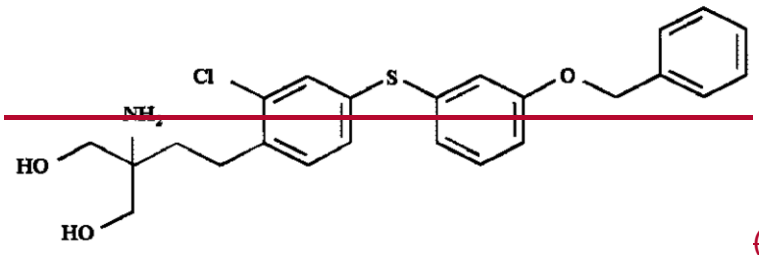


(a)

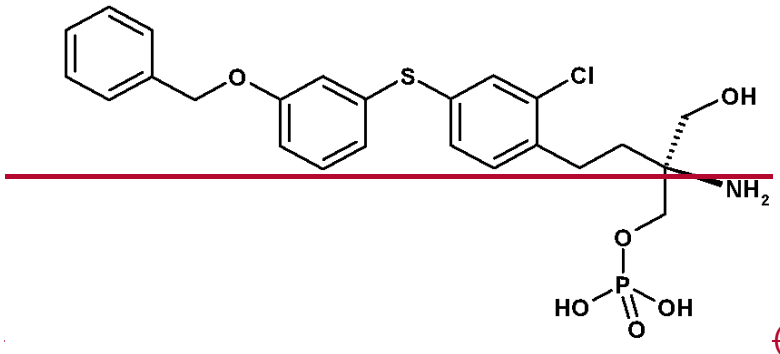
wherein each of R_8 and R_9, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

and n is an integer from 1 to 4; and

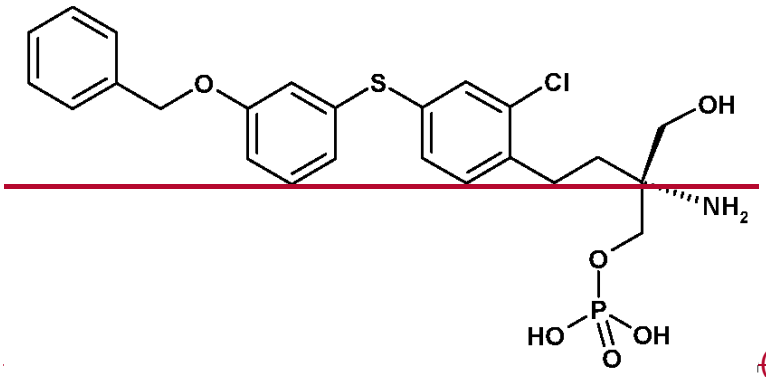
R_6 is hydrogen, halogen, C_{1-7}alkyl, C_{1-4}alkoxy or trifluoromethyl,



(II),



(IIa),



(IIb),

or pharmaceutically acceptable salts thereof.

4. The S1P receptor modulator, for use according to claim 18, wherein the S1P receptor agonist is mocravimod, or a pharmaceutically acceptable salt thereof.

4. The S1P receptor modulator for use according to any one of Claims 15-19, wherein said subject is selected among the patient population being either in first complete remission but in the adverse-risk group called “CR1 high risk”, or in second complete remission or beyond second relapse, called “CR2”, , wherein said CR1 high risk, CR2, patients are defined according to ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications of the American Society for Blood and Marrow Transplantation.

4. The S1P receptor modulator for use according to any one of claims 15-20, wherein said S1P receptor modulator is daily administered for at least 6, 7, 8, 9, 10, 11 or 12 months, or more, or until relapse, preferably from a starting day between 1-14 days prior to HSC transplant, preferably 11 days before HSCT.

4. The S1P receptor modulator for use according to any one of claims 15-21, wherein said S1P receptor modulator is mocravimod, and said subject is further treated with an efficient amount of immunosuppressants including at least cyclosporine A, and wherein said immunosuppressants treatment is reduced or stopped after at least 3 months, for example reduced to an amount of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% of the starting dose after at least 3 months.

4. The S1P receptor modulator for use according to any one of claims 15-22, wherein said subject is further administered an efficient amount of an immunosuppressant

~~essentially consisting of ciclosporin A, or of a combination of ciclosporin A and methotrexate.~~

~~4. The S1P receptor modulator for use according to claim 23, wherein said ciclosporin A is administered at a starting dose ranging between 2 to 6 mg/kg/day, preferably 3 to 5 mg/kg/day.~~

~~4. The S1P receptor modulator for use according to any one of claims 15-24, wherein said S1P receptor modulator is mocravimod, and said mocravimod is administered at a daily dose of 3mg.~~

~~4. The S1P receptor modulator for use according to any one of claims 15-24, wherein said S1P receptor modulator is mocravimod, and said mocravimod is administered at a daily dose of 1mg.~~

~~4. The S1P receptor modulator for use according to any one of claims 15-26, wherein said S1P receptor modulator is mocravimod, and said mocravimod is formulated as a solid dosage form, said solid dosage form comprising:~~

- ~~mannitol, preferably at a content from 48 to 88 mg/unit, more preferably from 58 to 78mg/unit, even more preferably at a content about 68 mg/unit;~~
- ~~microcrystalline cellulose, preferably at a content from 5 to 45 mg/unit, more preferably from 15 to 35 mg/unit, even more preferably at a content about 25 mg/unit;~~
- ~~sodium starch glycolate, preferably at a content from 1 to 8 mg/unit, more preferably from 2 to 6 mg/unit, even more preferably at a content about 4 mg/unit;~~
- ~~magnesium stearate, preferably at a content from 0.025 to 4 mg/unit, more preferably from 0.5 to 2 mg/unit, even more preferably at a content about 1 mg/unit; and~~
- ~~colloidal silicon dioxide, preferably at a content from 0.125 to 2 mg/unit, more preferably from 0.25 to 1 mg/unit, even more preferably at a content about 0.5 mg/unit.~~

4. A method of treating acute myelogenous leukemia in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT) comprising:

0) administering to the subject an effective amount of an S1P receptor modulator,

0) conditioning said subject for destroying substantially the bone marrow and immune system wherein said conditioning includes treatment of said subject with an effective amount of a chemotherapeutic agent and/or performing total body irradiation;

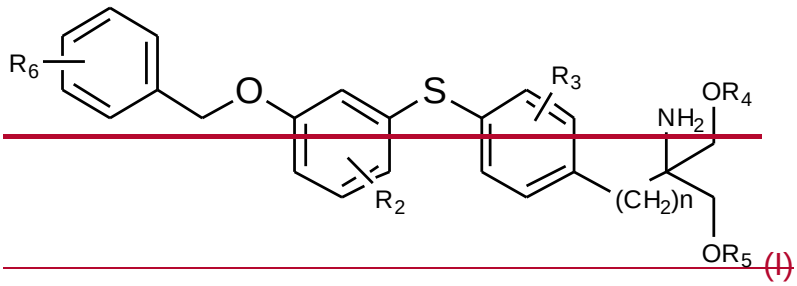
0) transplanting allogeneic hematopoietic stem cells from a donor to said subject; and,

0) optionally, co-administering an efficient amount of one or more immunosuppressants to prevent acute GVHD.

4. The method of claim 28, wherein said S1P receptor modulator is selected among mocravimod, FTY720, siponimod, fingolimod, ozanimod, ponesimod, etrasimod, AKP-11, cenerimod, amiselimod, CBP-307, OPL-307, OPL-002, BMS-986166, SCD-044, BOS-173717, CP-1050, preferably mocravimod.

4. The method of claim 29, wherein said S1P receptor modulator is a S1P receptor agonist.

4. The method of claim 29 or 30, wherein the S1P receptor modulator is of formula (I) or (II) or (IIa) or (IIb) :



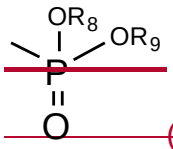
(I)

wherein

R_2 is H, halogen, trihalomethyl, C_{1-4}alkoxy, C_{1-7}alkyl, phenethyl or benzyloxy;

R_3 is H, halogen, CF_3, OH, C_{1-7}alkyl, C_{1-4}alkoxy, benzyloxy, phenyl or C_{1-4}alkoxymethyl;

each of R_4 and R_5, independently is H or a residue of formula (a)

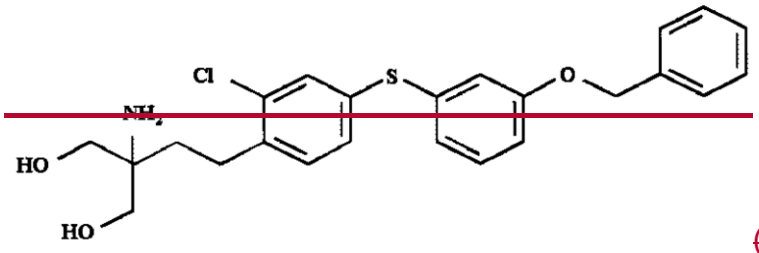


(a)

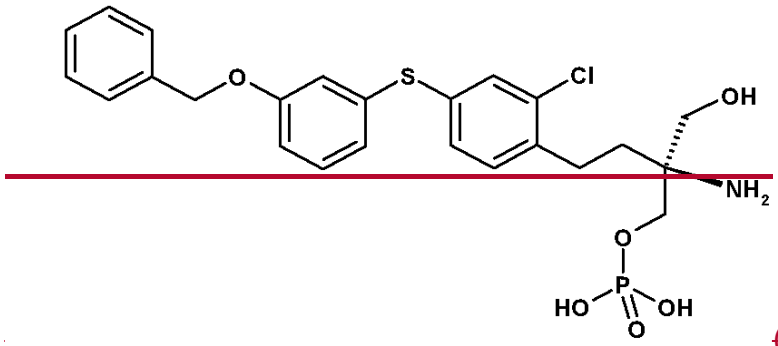
wherein each of R_8 and R_9, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

and n is an integer from 1 to 4; and

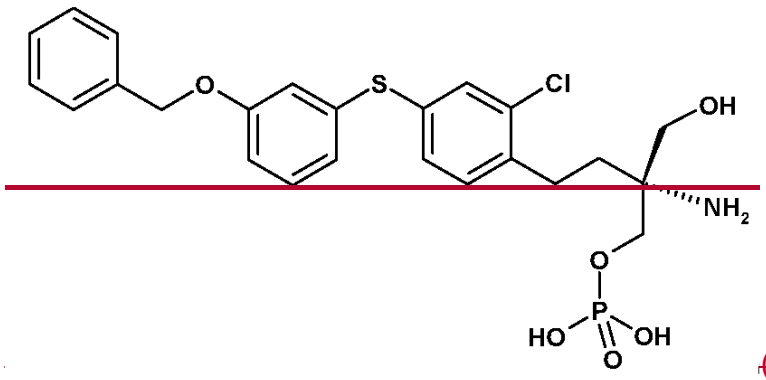
R_6 is hydrogen, halogen, C_{1-7}alkyl, C_{1-4}alkoxy or trifluoromethyl,



(II),



(IIa),



(IIb),

or pharmaceutically acceptable salts thereof, preferably mocravimod or pharmaceutically acceptable salts thereof.

4. The method of claims 28-31, wherein the administration of the S1P receptor modulator, preferably mocravimod, is started prior to allogenic HSCT, preferably at least 7 days prior to HSCT, more preferably 11 days prior to HSCT.

4. The method of claims 28-32, wherein the S1P receptor modulator, preferably mocravimod, is daily administered for a period set to at least 80 days, or at least 100 days or more, after the HSCT.

4. The method of claims 28-33, wherein the S1P receptor modulator, preferably mocravimod, is daily administered from 1 to 14 days prior to HSCT, preferably from 11 days prior to HSCT, for at least 12 months, or more, or until relapse.

4. The method of claims 28-34, wherein the S1P receptor modulator, preferably mocravimod, is administered per day at a fixed amount, preferably the fixed daily dosage is 0,05 mg to 40 mg per day, preferably 0,1 mg to 35 mg, more preferably 0,5 mg to 30 mg, even more preferably 1 mg to 15 mg per day, even more preferably 1,5 mg to 7mg, even more preferably 2 mg to 5 mg, even more preferably about 3 mg per day or about 1 mg per day.

4. The method of claims 28-35, wherein the S1P receptor modulator is mocravimod and said mocravimod is administered at a daily dose of 3mg, preferably three capsules a day of 1mg.

4. The method of claims 28-36, wherein the chemotherapeutic agent is selected from the group consisting of cyclophosphamide or thiotepa, cytarabine, etoposide, busulfan or melphalan, fludarabine, and mixtures thereof such as a combined administration of fludarabine/busulfan, busulfan/cyclophosphamide or fludarabine/melphalan.

4. The method of claims 28-37, wherein the conditioning regimen of step 2) consists in :

- the administration of cyclophosphamide followed by total body irradiation, or
- the administration of busulfan and cyclophosphamide, or

- the administration of fludarabine and busulfan, and optionally, total body irradiation with a low dosage.

4. The method of claims 28-38, wherein, in step 3), the hematopoietic stem cells are selected from HLA-matched related or unrelated donor with 8/8 or higher matches at the HLA-A, -B, -C, -DRB1, and/or –DQB1 loci, as determined by high resolution HLA typing.

4. The method of claims 28-39, wherein, in step 4), the one or more immunosuppressants is selected from the group consisting of ciclosporin A, sirolimus, tacrolimus, methotrexate, and mycophenolate, preferably ciclosporin A, or a mixture of ciclosporin A and methotrexate or tacrolimus or a mixture of tacrolimus and methotrexate.

4. The method of claim 40, wherein the immunosuppressant is at least ciclosporin A administered within a period between the starting day of administration of the S1P receptor modulator, preferably mocravimod, and the day of HSCT, preferably 3 days prior to HSCT.

4. The method of claim 40 or 41, wherein the ciclosporin A is administered intravenously at an initial dosage of 2.5 mg / kg over 2 hours every 12 hours and optionally adjusted between 150 to 400 mg / L.

4. The method of claims 40-42, wherein methotrexate is administered together with ciclosporin A at the day of HSCT at a dosage of 10 mg / kg of and optionally 2 and 5 days after the first administration and the 16th day therefrom, at a dosage of 6 mg / kg.

4. The method of claims 28-43, wherein the one or more immunosuppressants used in step 4) do not include tacrolimus.

4. The method of claims 28-44, wherein said S1P receptor modulator, preferably mocravimod, is administered for a period of at least 6 months, preferably 12, 18 or 24 months or more, or until relapse, said subject being further treated in step 4) with an efficient amount of immunosuppressants including at least ciclosporin A,

and said immunosuppressants treatment is reduced or stopped prior to 6 months following HSCT, preferably within a period from 3 to 6 months, or from 3 to 5 months, or from 3 to 4 months following HSCT.

4. The method of claim 45, wherein said immunosuppressants treatment is reduced of at least 10% compared to the starting dose of said immunosuppressants.

4. The method of any one of claims 28-46, wherein said subject is with refractory or relapsed AML after one or more AML therapy.

4. The method of claims 28-47, wherein said subject is selected among the patients suffering of acute myelogenous leukemia and being either in first complete remission but in the adverse-risk group called "CR1 high risk", or in second complete remission or beyond second relapse, (CR2), wherein said CR1 high risk, and CR2 patients are defined according to ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications of the American Society for Blood and Marrow Transplantation, preferably patients classified as CR1 high risk, and CR2.

4. The method of claims 28-48, wherein said S1P receptor modulator is administered in an amount sufficient to prevent acute GVHD.

4. The method of claims 28-49, wherein said S1P receptor modulator is administered in an amount sufficient to prevent acute and chronic GVHD.

4. The method of claims 28-50, wherein said patient is refractory GvHD-free and/or relapse free at 3 months from HSCT.

4. The method of claims 51, wherein, said patient does not present one or more of the following:

- grade III/IV acute graft-versus-host disease (GVHD) refractory to at least 2 lines of treatment
- extensive chronic GVHD refractory to systemic immunosuppressive treatment
- disease relapse
- death,

after at least 3 months from HSCT,

5. The method of claims 28-52, wherein said method improves morbidity or mortality in a population of subjects via refractory GVHD-free, relapse-free survival (rGRFS) and both relapse-related mortality and transplant-related mortality at least at 3 months from HSCT.

5. The method of claim 53, wherein said rGRFS patients represent at least 40% in the population of treated subjects.

5. The method of claim 53 which reduces the occurrence or severity of either GVHD, refractory chronic GVHD, relapse or mortality during the next 12 months after HSCT in a population of subjects.

5. The method of claims 28-55, wherein said method improves overall survival of a population of subjects.

5. The method of Claim 56, wherein the overall survival of a population of subjects is improved of at least 10, 15 or at least 20% as compared to the same method of HSCT without administration of said S1PR modulator compound.

5. The method of any one of claims 28-57, said method improves the quality of life of a population of subjects as compared to the same method of HSCT without administration of said S1PR modulator.

5. The method of claim 58, wherein the quality of life is measured according the Fundation for the Accreditation of Cellular Therapy Bone Marrow Transplantation (FACT-BMT) questionnaire and/or the MD Anderson symptom inventory (MDASI), at 3months or more.

5. The method of Claim 58 or 59, wherein the quality of life is improved by at least 10%.

5. A method of preventing chronic GvHD in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT) comprising:

0) administering to the subject an effective amount of an S1P receptor modulator,

0) conditioning said subject for destroying substantially the bone marrow and immune system wherein said conditioning includes treatment of said subject with an

effective amount of a chemotherapeutic agent and/or performing total body irradiation;

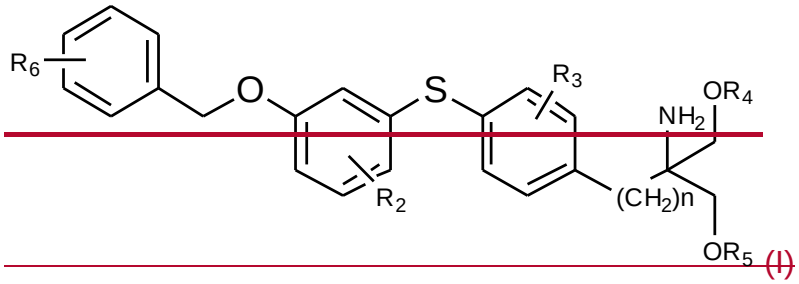
0) transplanting allogeneic hematopoietic stem cells from a donor to said subject; and,

0) optionally, co-administering an efficient amount of one or more immunosuppressants to prevent acute GVHD.

5. The method of claim 61, wherein the S1P receptor modulator is selected among mocravimod, FTY720, siponimod, fingolimod, ozanimod, ponesimod, etrasimod, AKP-11, cenerimod, amiselimod, CBP-307, OPL-307, OPL-002, BMS-986166, SCD-044, BOS-173717, CP-1050, preferably mocravimod.

5. The method of claim 62, wherein said S1P receptor modulator is a S1P receptor agonist.

5. The method of claim 62 or 63, wherein the S1P receptor modulator is of formula (I) or (II) or (IIa) or (IIb) :



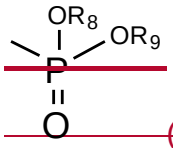
(I)

wherein

R_2 is H, halogen, trihalomethyl, C_{1-4}alkoxy, C_{1-7}alkyl, phenethyl or benzyloxy;

R_3 is H, halogen, CF_3, OH, C_{1-7}alkyl, C_{1-4}alkoxy, benzyloxy, phenyl or C_{1-4}alkoxymethyl;

each of R_4 and R_5, independently is H or a residue of formula (a)

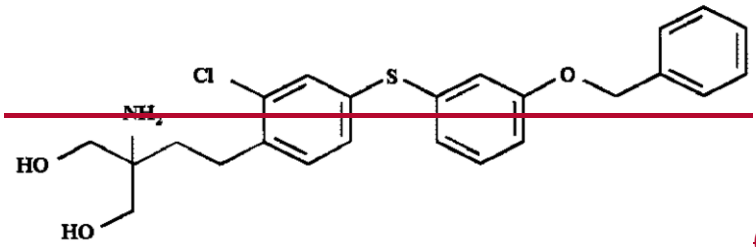


(a)

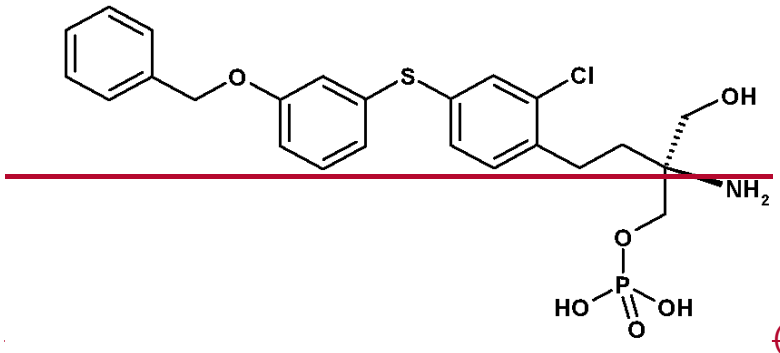
wherein each of R_8 and R_9, independently, is H or C_{1-4}alkyl optionally substituted by halogen;

and n is an integer from 1 to 4; and

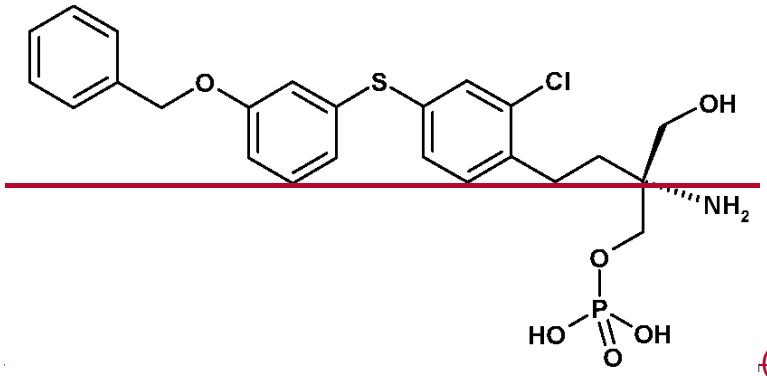
R_6 is hydrogen, halogen, C_{1-7}alkyl, C_{1-4}alkoxy or trifluoromethyl,



(II),



(IIa),



(IIb),

or pharmaceutically acceptable salts thereof, preferably mocravimod or pharmaceutically acceptable salts thereof.

5. The method of claims 61-64, wherein the administration of the S1P receptor modulator, preferably mocravimod, is started prior to allogenic HSCT, preferably from 1 to 14 days prior to HSCT, more preferably 11 days prior to HSCT.

5. The method of claims 61-65, wherein the S1P receptor modulator, preferably mocravimod, is daily administered for a period set to at least 80 days, or at least 100 days or more, after the HSCT.

5. The method of claims 61-66, wherein the S1P receptor modulator, preferably mocravimod, is daily administered from 1 to 14 days prior to HSCT, preferably from 11 days prior to HSCT, for at least 6 months, or more, or until relapse.

5. The method of claims 61-67, wherein the S1P receptor modulator, preferably mocravimod, is administered per day at a fixed amount, preferably the fixed daily dosage is 0,05 mg to 40 mg per day, preferably 0,1 mg to 35 mg, more preferably 0,5 mg to 30 mg, even more preferably 1 mg to 15 mg per day, even more preferably 1,5 mg to 7mg, even more preferably 2 mg to 5 mg, even more preferably about 3 mg per day or about 1 mg per day.

5. The method of claims 61-68, wherein the S1P receptor modulator is mocravimod and said mocravimod is administered at a daily dose of 3mg, preferably three capsules a day of 1mg.

5. The method of claims 61-69, wherein in step 2) the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, cytarabine, etoposide, busulfan, fludarabine, melphalan, methotrexate, cyclosporin A, and mixtures thereof such as fludarabine/busulfan, busulfan/cyclophosphamide and fludarabine/melphalan.

5. The method of claims 61-70, wherein in step 2) the treatment consists in :

- the administration of cyclophosphamide followed by total body irradiation, or
- the administration of busulfan and cyclophosphamide, or
- the administration of fludarabine and busulfan, and optionally, total body irradiation with a low dosage.

5. The method of claims 61-71, wherein in step 3) the hematopoietic stem cells are selected from HLA-matched related or unrelated donor with 8/8 or higher matches at the HLA-A, -B, -C, -DRB1, and/or –DQB1 loci, as determined by high resolution HLA typing.

6. The method of claims 61-72, wherein in step 4) the one or more immunosuppressants is selected from the group consisting of ciclosporin A, sirolimus, tacrolimus, methotrexate, and mycophenolate, preferably ciclosporin A or a combination of ciclosporin A and methotrexate or tacrolimus or a combination of tacrolimus and methotrexate.

6. The method of claim 73, wherein the immunosuppressant is at least ciclosporin A administered within a period between the starting day of administration of the S1P receptor modulator, preferably mocravimod, and the day of HSCT, preferably 3 days prior to HSCT.

6. The method of claim 73 or 74, wherein the ciclosporin A is administered intravenously at an initial dosage of 2.5 mg / kg over 2 hours every 12 hours and optionally adjusted between 150 to 400 mg / L.

6. The method of claims 73-75, wherein methotrexate is administered together with ciclosporin A the day of HSCT at a dosage of 10 mg / kg of and optionally 2 and 5 days after the first administration and the 16th day therefrom, at a dosage of 6 mg/kg.

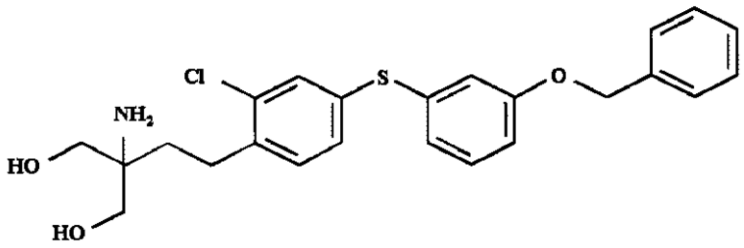
6. The method of claims 73-76, wherein the one or more immunosuppressants used in step 4) do not include tacrolimus.

6. The method of claims 73-77, wherein in step 1) the S1P receptor modulator, preferably mocravimod, is daily administered for at least 6 months, preferably 12, 18 or 24 months or more, or until relapse, said subject being further treated in step 4) with an efficient amount of immunosuppressants including at least ciclosporin A, and said immunosuppressants treatment is reduced or stopped prior to 6 months following HSCT, preferably within a period from 3 to 6 months, or from 3 to 5 months, or from 3 to 4 months following HSCT.

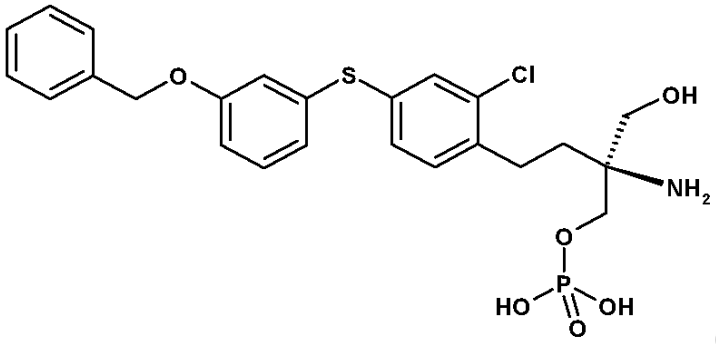
6. The method of claim 78, wherein said immunosuppressants treatment is reduced of about 10% or more compared to the starting dose of said immunosuppressant.

~~7. The method of claims 73-79, wherein said subject is selected among the patients suffering of acute myelogenous leukemia and being either in first complete remission but in the adverse-risk group called (CR1 high risk), or in second complete remission or beyond second relapse (CR2), wherein said CR1 high risk, and CR2 patients are defined according to ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications of the American Society for Blood and Marrow Transplantation, preferably patients classified as CR1 high risk and CR2.~~

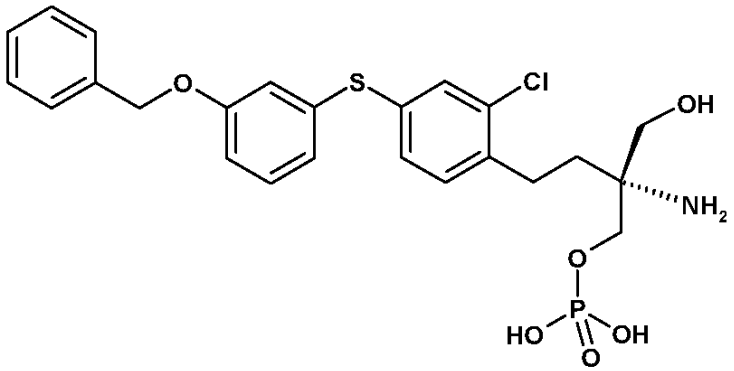
~~8.~~1. A pharmaceutical composition comprising an S1P receptor modulator of formula (II) or formula (IIa) or formula (IIb):



(II),



(IIa),



(IIb),

or pharmaceutically acceptable salts thereof,

characterized in that the dosage strength of the S1P receptor modulator, preferably the hydrochloride salt of formula (II), in the solid dosage form unit is about 1 mg/unit, and comprising

~~at least one filler selected from mannitol, microcrystalline cellulose and mixtures thereof, sodium starch glycolate as disintegrant, magnesium stearate as lubricant and, colloidal silicon dioxide as glidant~~

- mannitol at a content from 48 to 88 mg/unit, preferably from 58 to 78mg/unit, more preferably at a content about 68 mg/unit;
- microcrystalline cellulose at a content from 5 to 45 mg/unit, preferably from 15 to 35 mg/unit, more preferably at a content about 25 mg/unit;
- sodium starch glycolate at a content from 1 to 8 mg/unit, preferably from 2 to 6 mg/unit, more preferably at a content about 4 mg/unit;
- magnesium stearate at a content from 0.025 to 4 mg/unit, preferably from 0.5 to 2 mg/unit, more preferably at a content about 1 mg/unit; and
- colloidal silicon dioxide at a content from 0.125 to 2 mg/unit, preferably from 0.25 to 1 mg/unit, more preferably at a content about 0.5 mg/unit.

~~9.~~2. The pharmaceutical composition of claim ~~8~~1, ~~wherein~~ characterized in that the S1P receptor modulator is the hydrochloride salt of formula (II).

~~9. The pharmaceutical composition of claim 81 or 82, wherein the filler is a mixture of mannitol and microcrystalline cellulose.~~

~~10.~~3. The pharmaceutical composition of claim~~s~~ ~~81 to 83~~1 or 2, characterized in that ~~wherein~~ the composition is a solid dosage form suitable for oral administration selected from capsules, tablets, pills, powders, and granules, preferably capsules or tablets.

~~11.~~4. The pharmaceutical composition of claims ~~8~~1 to ~~84~~3, characterized in that ~~wherein~~ the solid dosage form is immediate or modified such as delayed, targeted or extended, preferably an immediate release dosage form.

~~12. The pharmaceutical composition of claims 81 to 85, wherein the dosage strength of the S1P receptor modulator, preferably the hydrochloride salt of formula (II), in the solid dosage form unit is between 0.05 mg to 15 mg/unit, preferably~~

~~between 0.1mg to 10mg/unit, for example about 0.1mg/unit, or about 0.4mg/unit, or about 1 mg/unit, or about 10 mg/unit, more preferably about 1 mg/unit.~~

~~14. The pharmaceutical composition of claims 81 to 86 which comprises:~~

~~- mannitol at a content from 48 to 88 mg/unit, preferably from 58 to 78mg/unit, more preferably at a content about 68 mg/unit;~~

~~- microcrystalline cellulose at a content from 5 to 45 mg/unit, preferably from 15 to 35 mg/unit, more preferably at a content about 25 mg/unit;~~

~~- sodium starch glycolate at a content from 1 to 8 mg/unit, preferably from 2 to 6 mg/unit, more preferably at a content about 4 mg/unit;~~

~~- magnesium stearate at a content from 0.025 to 4 mg/unit, preferably from 0.5 to 2 mg/unit, more preferably at a content about 1 mg/unit; and~~

~~- colloidal silicon dioxide at a content from 0.125 to 2 mg/unit, preferably from 0.25 to 1 mg/unit, more preferably at a content about 0.5 mg/unit.~~

~~21.~~5. The pharmaceutical composition of claims ~~8~~1 to ~~87~~4, characterized in that ~~wherein~~ the S1P receptor modulator has an average particle size of less than or equal to 8µm, preferably 6µm, more preferably 5µm and/or a D90 of less than or equal to 25µm, preferably 22µm, more preferably 18µm.

~~22.~~6. The pharmaceutical composition of claims ~~8~~1 to ~~88~~5, characterized in that said pharmaceutical composition ~~which~~ is stable for at least 24 months at 25°C.

~~23.~~7. A process of preparing the pharmaceutical composition according to claims ~~8~~1 to ~~89~~6, characterized in that ~~wherein~~ said process comprises the step of:

a. Blending the S1P receptor modulator with microcrystalline cellulose, colloidal silicon dioxide,
b. adding mannitol and blending the resulting mixture,
c. adding sodium starch glycolate and blending the resulting mixture,
d. adding magnesium stearate, blending the resulting pharmaceutical composition,
e. recovering the pharmaceutical composition.

~~24.~~8. The process of claim ~~90~~7, characterized in that ~~wherein~~ it further comprises the step of:

f. filling the resulting pharmaceutical composition into capsules,

g. recovering the resulting capsules filled with the pharmaceutical composition.

25. A method of treating acute myelogenous leukemia in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT) comprising:

1) administering to the subject an effective amount of mocravimod,

2) conditioning said subject for destroying substantially the bone marrow and immune system wherein said conditioning includes treatment of said subject with an effective amount of a chemotherapeutic agent and/or performing total body irradiation;

3) transplanting allogeneic hematopoietic stem cells from a donor to said subject; and,

4) optionally, co-administering an efficient amount of one or more immunosuppressants to prevent acute GVHD.

26. The method of claim 92, wherein the administration of mocravimod is started prior to allogenic HSCT, preferably at least 7 days prior to HSCT, more preferably 11 days prior to HSCT.

27. The method of claim 92 or 93, wherein mocravimod is daily administered for a period set to at least 80 days, or at least 100 days or more, after the HSCT.

28. The method of claims 92-94, wherein mocravimod is daily administered from 1 to 14 days prior to HSCT, preferably from 11 days prior to HSCT, for at least 12 months, or more, or until relapse.

29. The method of claims 92-95, wherein mocravimod is administered per day at a fixed amount, preferably the fixed daily dosage is 0,05 mg to 40 mg per day, preferably 0,1 mg to 35 mg, more preferably 0,5 mg to 30 mg, even more preferably 1 mg to 15 mg per day, even more preferably 1,5 mg to 7mg, even more preferably 2 mg to 5 mg, even more preferably about 3 mg per day or about 1 mg per day.

30. The method of claims 92-96, wherein mocravimod is administered at a daily dose of about 3mg, preferably three capsules a day of 1mg.

31. The method of claims 92-96, wherein mocravimod is administered at a daily dose of about 1mg.

32. The method of claims 92-98, wherein the chemotherapeutic agent is selected from the group consisting of cyclophosphamide or thiotepa, cytarabine, etoposide, busulfan or melphalan, fludarabine, and mixtures thereof such as a combined administration of fludarabine/busulfan, busulfan/cyclophosphamide or fludarabine/melphalan.

~~33. The method of claims 92-99, wherein the conditioning regimen of step 2) consists in :~~

~~- the administration of cyclophosphamide followed by total body irradiation, or~~

~~- the administration of busulfan and cyclophosphamide, or~~

~~- the administration of fludarabine and busulfan, and optionally, total body irradiation with a low dosage.~~

~~34. The method of claims 92-100, wherein, in step 3), the hematopoietic stem cells are selected from HLA-matched related or unrelated donor with 8/8 or higher matches at the HLA-A, -B, -C, -DRB1, and/or –DQB1 loci, as determined by high resolution HLA typing.~~

~~35. The method of claims 92-101, wherein, in step 4), the one or more immunosuppressants is selected from the group consisting of ciclosporin A, sirolimus, tacrolimus, methotrexate, and mycophenolate, preferably ciclosporin A, or a mixture of ciclosporin A and methotrexate or tacrolimus or a mixture of tacrolimus and methotrexate.~~

~~36. The method of claim 102, wherein the immunosuppressant is at least ciclosporin A administered within a period between the starting day of mocravimod, and the day of HSCT, preferably 3 days prior to HSCT.~~

~~37. The method of claim 102 or 103, wherein the ciclosporin A is administered intravenously at an initial dosage of 2.5 mg / kg over 2 hours every 12 hours and optionally adjusted between 150 to 400 mg / L.~~

~~38. The method of claims 102-104, wherein methotrexate is administered together with ciclosporin A at the day of HSCT at a dosage of 10 mg / kg of and optionally 2 and 5 days after the first administration and the 16th day therefrom, at a dosage of 6 mg / kg.~~

~~39. The method of claims 102-105, wherein the one or more immunosuppressants used in step 4) do not include tacrolimus.~~

~~40. The method of claims 102-106, wherein said mocravimod, is administered for a period of at least 6 months, preferably 12, 18 or 24 months or more, or until relapse, said subject being further treated in step 4) with an efficient amount of immunosuppressants including at least ciclosporin A, and said immunosuppressants treatment is reduced or stopped prior to 6 months following HSCT, preferably within a period from 3 to 6 months, or from 3 to 5 months, or from 3 to 4 months following HSCT.~~

41. The method of claim 107, wherein said immunosuppressants treatment is reduced of at least 10% compared to the starting dose of said immunosuppressants.

42. The method of any one of claims 92-108, wherein said subject is with refractory or relapsed AML after one or more AML therapy.

43. The method of claims 92-109, wherein said subject is selected among the patients suffering of acute myelogenous leukemia and being either in first complete remission but in the adverse-risk group called "CR1 high risk", or in second complete remission or beyond second relapse, (CR2), wherein said CR1 high risk, and CR2 patients are defined according to ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications of the American Society for Blood and Marrow Transplantation, preferably patients classified as CR1 high risk, and CR2.

44. The method of claims 92-110, wherein said mocravimod is administered in an amount sufficient to prevent acute GVHD.

45. The method of claims 92-111, wherein said mocravimod is administered in an amount sufficient to prevent acute and chronic GVHD.

46. The method of claims 92-112, wherein said patient is refractory GvHD-free and/or relapse free at 3 months from HSCT.

47. The method of claims 113, wherein, said patient does not present one or more of the following:

- grade III/IV acute graft-versus-host disease (GVHD) refractory to at least 2 lines of treatment
- extensive chronic GVHD refractory to systemic immunosuppressive treatment
- disease relapse
- death,

after at least 3 months from HSCT,

48. The method of claims 92-114, wherein said method improves morbidity or mortality in a population of subjects via refractory GVHD-free, relapse-free survival (rGRFS) and both relapse-related mortality and transplant-related mortality at least at 3 months from HSCT.

49. The method of claim 115, wherein said rGRFS patients represent at least 40% in the population of treated subjects.

50. The method of claim 115, which reduces the occurrence or severity of either GVHD, refractory chronic GVHD, relapse or mortality during the next 12 months after HSCT in a population of subjects.

51. The method of claims 92-117, wherein said method improves overall survival of a population of subjects.

52. The method of Claim 118, wherein the overall survival of a population of subjects is improved of at least 10, 15 or at least 20% as compared to the same method of HSCT without administration of said mocravimod.

53. The method of any one of claims 92-119, said method improves the quality of life of a population of subjects as compared to the same method of HSCT without administration of said S1PR modulator.

54. The method of claim 120, wherein the quality of life is measured according the Fundation for the Accreditation of Cellular Therapy Bone Marrow Transplantation (FACT-BMT) questionnaire and/or the MD Anderson symptom inventory (MDASI), at 3months or more.

55. The method of Claim 120 or 121, wherein the quality of life is improved by at least 10%.

56. A method of preventing chronic GvHD in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT) comprising:

1) administering to the subject an effective amount of mocravimod,

2) conditioning said subject for destroying substantially the bone marrow and immune system wherein said conditioning includes treatment of said subject with an effective amount of a chemotherapeutic agent and/or performing total body irradiation;

3) transplanting allogeneic hematopoietic stem cells from a donor to said subject; and,

4) optionally, co-administering an efficient amount of one or more immunosuppressants to prevent acute GVHD.

57. The method of claims 123, wherein the administration of mocravimod, is started prior to allogenic HSCT, preferably from 1 to 14 days prior to HSCT, more preferably 11 days prior to HSCT.

~~58. The method of claim 123 or 124, wherein mocravimod is daily administered for a period set to at least 80 days, or at least 100 days or more, after the HSCT.~~

~~59. The method of claims 123-125, wherein mocravimod is daily administered from 1 to 14 days prior to HSCT, preferably from 11 days prior to HSCT, for at least 6 months, or more, or until relapse.~~

~~60. The method of claims 123-126, wherein mocravimod is administered per day at a fixed amount, preferably the fixed daily dosage is 0,05 mg to 40 mg per day, preferably 0,1 mg to 35 mg, more preferably 0,5 mg to 30 mg, even more preferably 1 mg to 15 mg per day, even more preferably 1,5 mg to 7mg, even more preferably 2 mg to 5 mg, even more preferably about 3 mg per day or about 1 mg per day.~~

~~61. The method of claims 123-127, wherein mocravimod is administered at a daily dose of about 3mg, preferably three capsules a day of 1mg.~~

~~62. The method of claims 123-127, wherein mocravimod is administered at a daily dose of about 1 mg.~~

~~63. The method of claims 123-129, wherein in step 2) the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, cytarabine, etoposide, busulfan, fludarabine, melphalan, methotrexate, cyclosporin A, and mixtures thereof such as fludarabine/busulfan, busulfan/cyclophosphamide and fludarabine/melphalan.~~

~~64. The method of claims 123-130, wherein in step 2) the treatment consists in :~~

- ~~the administration of cyclophosphamide followed by total body irradiation, or~~
- ~~the administration of busulfan and cyclophosphamide, or~~
- ~~the administration of fludarabine and busulfan, and optionally, total body irradiation with a low dosage.~~

~~65. The method of claims 123-131, wherein in step 3) the hematopoietic stem cells are selected from HLA-matched related or unrelated donor with 8/8 or higher matches at the HLA-A, -B, -C, -DRB1, and/or –DQB1 loci, as determined by high resolution HLA typing.~~

~~66. The method of claims 123-132, wherein in step 4) the one or more immunosuppressants is selected from the group consisting of ciclosporin A, sirolimus, tacrolimus, methotrexate, and mycophenolate, preferably ciclosporin A or a combination of ciclosporin A and methotrexate or tacrolimus or a combination of tacrolimus and methotrexate.~~

67. The method of claim 133, wherein the immunosuppressant is at least ciclosporin A administered within a period between the starting day of administration of mocravimod, and the day of HSCT, preferably 3 days prior to HSCT.

68. The method of claim 133 or 134, wherein the ciclosporin A is administered intravenously at an initial dosage of 2.5 mg / kg over 2 hours every 12 hours and optionally adjusted between 150 to 400 mg / L.

69. The method of claims 133-135, wherein methotrexate is administered together with ciclosporin A the day of HSCT at a dosage of 10 mg / kg of and optionally 2 and 5 days after the first administration and the 16th day therefrom, at a dosage of 6 mg/kg.

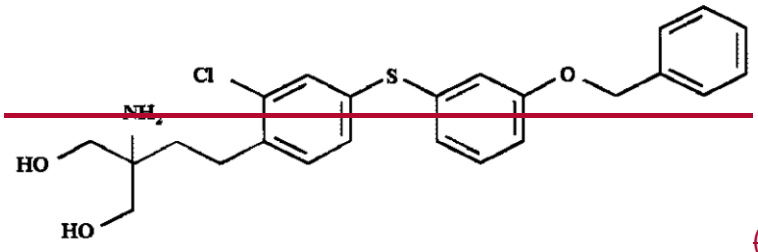
70. The method of claims 133-136, wherein the one or more immunosuppressants used in step 4) do not include tacrolimus.

71. The method of claims 133-137, wherein in step 1) mocravimod, is daily administered for at least 6 months, preferably 12, 18 or 24 months or more, or until relapse, said subject being further treated in step 4) with an efficient amount of immunosuppressants including at least ciclosporin A, and said immunosuppressants treatment is reduced or stopped prior to 6 months following HSCT, preferably within a period from 3 to 6 months, or from 3 to 5 months, or from 3 to 4 months following HSCT.

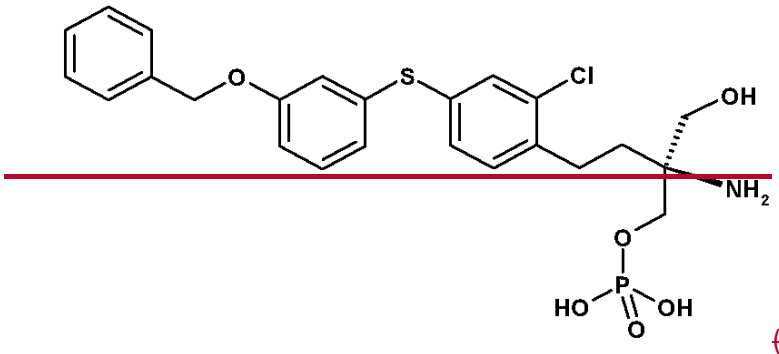
72. The method of claim 138, wherein said immunosuppressants treatment is reduced of about 10% or more compared to the starting dose of said immunosuppressant.

73. The method of claims 133-139, wherein said subject is selected among the patients suffering of acute myelogenous leukemia and being either in first complete remission but in the adverse-risk group called (CR1 high risk), or in second complete remission or beyond second relapse (CR2), wherein said CR1 high risk, and CR2 patients are defined according to ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications of the American Society for Blood and Marrow Transplantation, preferably patients classified as CR1 high risk and CR2.

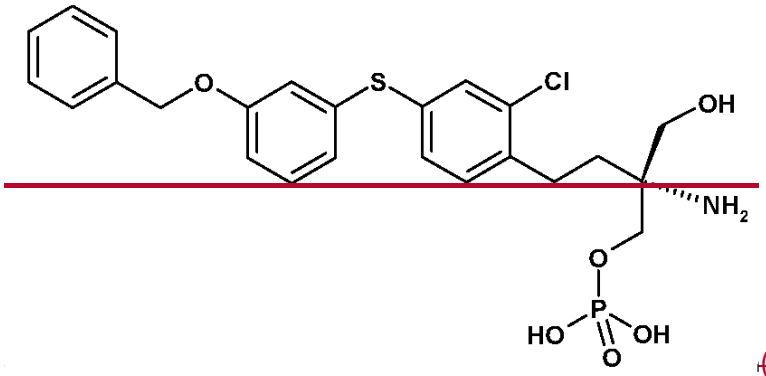
74. A pharmaceutical composition comprising an S1P receptor modulator of formula (II) or formula (IIa) or formula (IIb):



~~(II),~~



~~(IIa),~~



~~(IIb),~~

~~or pharmaceutically acceptable salts thereof, for use in treating acute myelogenous leukemia (AML) in a subject undergoing allogeneic hematopoietic stem cell transplant (HSCT) wherein the composition comprises at least one filler selected from mannitol, microcrystalline cellulose and mixtures thereof, sodium starch glycolate as disintegrant, magnesium stearate as lubricant and, colloidal silicon dioxide as glidant.~~

~~75. The pharmaceutical composition of claim 141, wherein the S1P receptor modulator is the hydrochloride salt of formula (II).~~

~~76. The pharmaceutical composition of claim 141 or 142, wherein the filler is a mixture of mannitol and microcrystalline cellulose.~~

~~77. The pharmaceutical composition of claims 141-143, wherein the composition is a solid dosage form suitable for oral administration selected from capsules, tablets, pills, powders, and granules, preferably capsules or tablets.~~

78. The pharmaceutical composition of claims 141-144, wherein the solid dosage form is immediate or modified such as delayed, targeted or extended, preferably an immediate release dosage form.

79. The pharmaceutical composition of claims 141-145, wherein the dosage strength of the S1P receptor modulator, preferably the hydrochloride salt of formula (II), in the solid dosage form unit is between 0.05 mg to 15 mg/unit, preferably between 0.1mg to 10mg/unit, for example about 0.1mg/unit, or about 0.4mg/unit, or about 1 mg/unit, or about 10 mg/unit, more preferably about 1 mg/unit.

80. The pharmaceutical composition of claims 141-146 which comprises:

- mannitol at a content from 48 to 88 mg/unit, preferably from 58 to 78mg/unit, more preferably at a content about 68 mg/unit;

- microcrystalline cellulose at a content from 5 to 45 mg/unit, preferably from 15 to 35 mg/unit, more preferably at a content about 25 mg/unit;

- sodium starch glycolate at a content from 1 to 8 mg/unit, preferably from 2 to 6 mg/unit, more preferably at a content about 4 mg/unit;

- magnesium stearate at a content from 0.025 to 4 mg/unit, preferably from 0.5 to 2 mg/unit, more preferably at a content about 1 mg/unit; and

- colloidal silicon dioxide at a content from 0.125 to 2 mg/unit, preferably from 0.25 to 1 mg/unit, more preferably at a content about 0.5 mg/unit.

81. The pharmaceutical composition of claims 141-147, wherein the S1P receptor modulator is administered per day at a fixed amount, preferably the fixed daily dosage is 0,05 mg to 40 mg per day, preferably 0,1 mg to 35 mg, more preferably 0,5 mg to 30 mg, even more preferably 1 mg to 15 mg per day, even more preferably 1,5 mg to 7mg, even more preferably 2 mg to 5 mg, even more preferably about 3 mg per day or about 1 mg per day.

82. The pharmaceutical composition of claims 141-148, wherein said S1P receptor modulator is administered at a daily dose of about 3mg, preferably three capsules a day of 1mg.

83. The pharmaceutical composition of claims 141-149, wherein said S1P receptor modulator is administered at a daily dose of about 1 mg.

84. The pharmaceutical composition of claims 141-150, wherein said S1P receptor modulator is daily administered for at least 6 months, preferably 12, 18 or 24 months or more.

85. The pharmaceutical composition of claims 141-151, wherein it comprises:

- mannitol at a content about 68 mg/unit;

- microcrystalline cellulose at a content about 25 mg/unit;

- ~~sodium starch glycolate at a content about 4 mg/unit;~~
- ~~magnesium stearate at a content about 1 mg/unit; and~~
- ~~colloidal silicon dioxide at a a content about 0.5 mg/unit.~~

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