

(Kisseleva et al., 2002, *Gene* 285:1-24; Levy et al., 2005, *Nat. Rev. Mol. Cell Biol.* 3:651-662; O'Shea et al., 2002, *Cell*, 109 (suppl.): S121-S131). Consistent with this, JAK2 knockout mice die of anemia (O'Shea et al., 2002, *Cell*, 109 (suppl.): S121-S131). Kinase activating mutations in JAK2 (e.g., JAK2 V617F) are associated with myeloproliferative disorders in humans.

JAK3 associates exclusively with the gamma common cytokine receptor chain, which is present in the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokine receptor complexes. JAK3 is critical for lymphoid cell development and proliferation and mutations in JAK3 result in severe combined immunodeficiency (SCID) (O'Shea et al., 2002, *Cell*, 109 (suppl.): S121-S131). Based on its role in regulating lymphocytes, JAK3 and JAK3-mediated pathways have been targeted for immunosuppressive indications (e.g., transplantation rejection and rheumatoid arthritis) (Baslund et al., 2005, *Arthritis & Rheumatism* 52:2686-2692; Changelian et al., 2003, *Science* 302: 875-878).

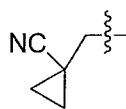
TYK2 associates with the type I interferon (e.g., IFN α), IL-6, IL-10, IL-12 and IL-23 cytokine receptor complexes (Kisseleva et al., 2002, *Gene* 285:1-24; Watford, W.T. & O'Shea, J.J., 2006, *Immunity* 25:695-697). Consistent with this, primary cells derived from a TYK2 deficient human are defective in type I interferon, IL-6, IL-10, IL-12 and IL-23 signaling. A fully human monoclonal antibody targeting the shared p40 subunit of the IL-12 and IL-23 cytokines (Ustekinumab) was recently approved by the European Commission for the treatment of moderate-to-severe plaque psoriasis (Krueger et al., 2007, *N. Engl. J. Med.* 356:580-92; Reich et al., 2009, *Nat. Rev. Drug Discov.* 8:355-356). In addition, an antibody targeting the IL-12 and IL-23 pathways underwent clinical trials for treating Crohn's Disease (Mannon et al., 2004, *N. Engl. J. Med.* 351:2069-79).

There exists a need in the art for additional or alternative treatments of conditions mediated by JAK kinases, such as those described above.

SUMMARY

Provided herein are JAK kinase inhibitory compounds. Accordingly, one aspect of the present disclosure includes a compound of Formula (I) or (II):

heteroaryl optionally substituted by C1-C6 alkyl), -(C0-C6 alkylene)-(3-7 membered heterocycloalkyl optionally substituted by C1-C6 alkyl or 3-7 membered heterocycloalkyl) and



; and

5 R^c is 3-10 membered cycloalkyl, 3-10 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl, wherein R^c is optionally substituted by halogen, CN, OH, C1-C6 alkyl optionally substituted by halogen, OH, CN, C1-C6 alkoxy or C1-C6 thioalkyl, C1-C6 alkoxy optionally substituted by halogen, C1-C6 thioalkyl optionally substituted by halogen, -(C0-C6 alkylene)- NR^aR^b , -(C0-C6 alkylene)-3-7 membered
10 cycloalkyl, -(C0-C6 alkylene)-(3-10 membered heterocycloalkyl optionally substituted by halogen, OH, CN, C1-C6 alkyl or C1-C6 haloalkyl), -(C0-C6 alkylene)-(phenyl optionally substituted by halogen, OH, CN, C1-C6 alkyl or C1-C6 haloalkyl) or -(C0-C6 alkylene)-(5-6 membered heteroaryl optionally substituted by halogen, OH, CN, C1-C6 alkyl or C1-C6 haloalkyl).

15 Also provided are pharmaceutical compositions comprising a compound of Formula (I) or (II), or a stereoisomer, tautomer, solvate, prodrug or salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient. Another aspect of the present disclosure includes a pharmaceutical composition comprising a compound as defined herein, or a stereoisomer, tautomer, solvate, prodrug or salt thereof and a
20 pharmaceutically acceptable carrier, diluent or excipient.

Yet another aspect of the present disclosure includes a compound as defined herein, or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use in therapy. A further aspect of the present disclosure includes a compound as defined herein, or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use in the treatment of an
25 inflammatory disease. The present disclosure also provides, in some embodiments, use a compound of Formula (I) or (II) or a stereoisomer, tautomer, solvate, prodrug or salt thereof, in therapy, such as in the treatment of an inflammatory disease. Another aspect of the present disclosure includes the use of a compound as defined herein, or a stereoisomer, tautomer, solvate, prodrug or salt thereof for the preparation of a
30 medicament for the treatment of an inflammatory disease. Also provided are uses of a compound of Formula (I) or (II), or a stereoisomer, tautomer, solvate, prodrug or salt thereof, for the preparation of a

medicament for the treatment of an inflammatory disease, such as asthma. Also provided is a method of preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of a Janus kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or (II) or a stereoisomer, tautomer, solvate, prodrug or salt thereof. Another aspect of the present disclosure includes a compound of Formula (I) or (II), or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use in preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of a Janus kinase activity in a patient.

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Detailed Description of the Invention

DEFINITIONS

“Halogen” or “halo” refers to F, Cl, Br or I. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl.

26. A pharmaceutical composition comprising a compound of any of claims 1-25 or a stereoisomer, tautomer, solvate, prodrug or salt thereof and a pharmaceutically acceptable carrier, diluent or excipient.
27. A compound of any of claims 1-25 or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use in therapy.
28. Use of a compound of any of claims 1-25 or a stereoisomer, tautomer, solvate, prodrug or salt thereof for the preparation of a medicament for the treatment of an inflammatory disease.
29. A compound of any of claims 1-25 or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use in the treatment of an inflammatory disease.
30. The use of claim 28 or the compound of claim 29 or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the inflammatory disease is asthma.
31. A compound of any of claims 1-25 or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use in preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of a Janus kinase activity in a patient.
32. The compound or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use according to claim 31, wherein the disease or condition is asthma.
33. The compound or a stereoisomer, tautomer, solvate, prodrug or salt thereof for use according to claim 31, wherein the Janus kinase is JAK1.