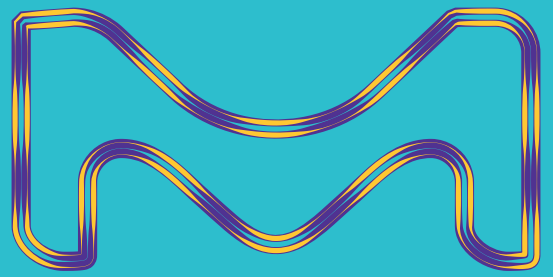
EMD Serono
Neurology pipeline

Pipeline products are under clinical investigation and have not been proven safe or effective. There is no guarantee that any product will be approved in the sought-after indication.



EMD Serono is a business of Merck KGaA, Darmstadt, Germany

US-NON-0716-0020(2)

EMD Serono

EMD Serono pipeline

November 7th, 2016

Phase I

tepotinib
c-Met kinase inhibitor
Solid tumors

M2698
p70S6K & Akt inhibitor
Solid tumors

M3814
DNA-PK inhibitor
Solid tumors

Beigene-283
BRAF inhibitor
Solid tumors

M7583
BTK inhibitor
Hematological Malignancies

avelumab
anti-PD-L1 mAb
Solid tumors

avelumab
anti-PD-L1 mAb
Hematological Malignancies

M9241 (NHS-IL12)
Cancer immunotherapy
Solid tumors

M7824
anti-PD-L1/TGFbeta trap
Solid tumors

M1095 (ALX-0761)
anti-IL-17 A/F nanobody
Psoriasis

M2951
BTK inhibitor
Systemic lupus erythematosus

Phase II

tepotinib
c-Met kinase inhibitor
Non-small cell lung cancer

tepotinib
c-Met kinase inhibitor
Hepatocellular cancer

sprifermin
Fibroblast growth factor 18
Osteoarthritis

atacicept
anti-Blys/anti-APRIL fusion protein
Systemic lupus erythematosus

M2951
BTK inhibitor
Rheumatoid Arthritis

Phase III

avelumab - anti-PD-L1 mAb
Non-small cell lung cancer 1L[1]

avelumab - anti-PD-L1 mAb
Non-small cell lung cancer 2L[2]

avelumab - anti-PD-L1 mAb
Gastric cancer 1L[1]

avelumab - anti-PD-L1 mAb
Gastric cancer 3L[3]

avelumab - anti-PD-L1 mAb
Bladder cancer 1L[1]

avelumab - anti-PD-L1 mAb
Ovarian cancer platinum resistant/refractory

avelumab - anti-PD-L1 mAb
Ovarian cancer 1L[1]

avelumab - anti-PD-L1 mAb
Renal cell cancer 1L[1]

MSB 11022
proposed biosimilar of adalimumab
Chronic Plaque Psoriasis

Registration

cladribine tablets[4]
lymphocyte targeting agent
Relapsing-remitting multiple sclerosis

avelumab[5]
anti-PD-L1 mAb
Merkel cell carcinoma

- Neurodegenerative Diseases
- Oncology
- Immunology
- Immuno-Oncology
- Biosimilars

[1] First Line treatment
[2] Second Line treatment
[3] Third Line treatment
[4] As announced on July 18th, 2016 the European Medicines Agency accepted Merck KGaA, Darmstadt, Germany's Marketing Authorization Application
[5] European Medicines Agency accepted Merck KGaA, Darmstadt, Germany's Marketing Authorization Application in October 2016

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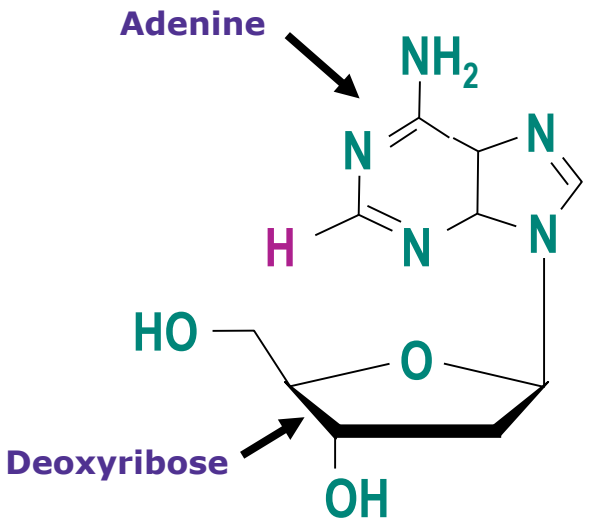
01

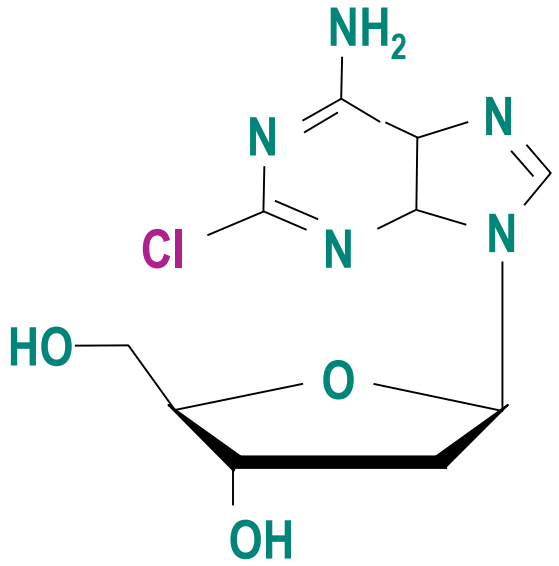
cladribine tablets overview

Molecular structure of cladribine



Deoxyadenosine[3]

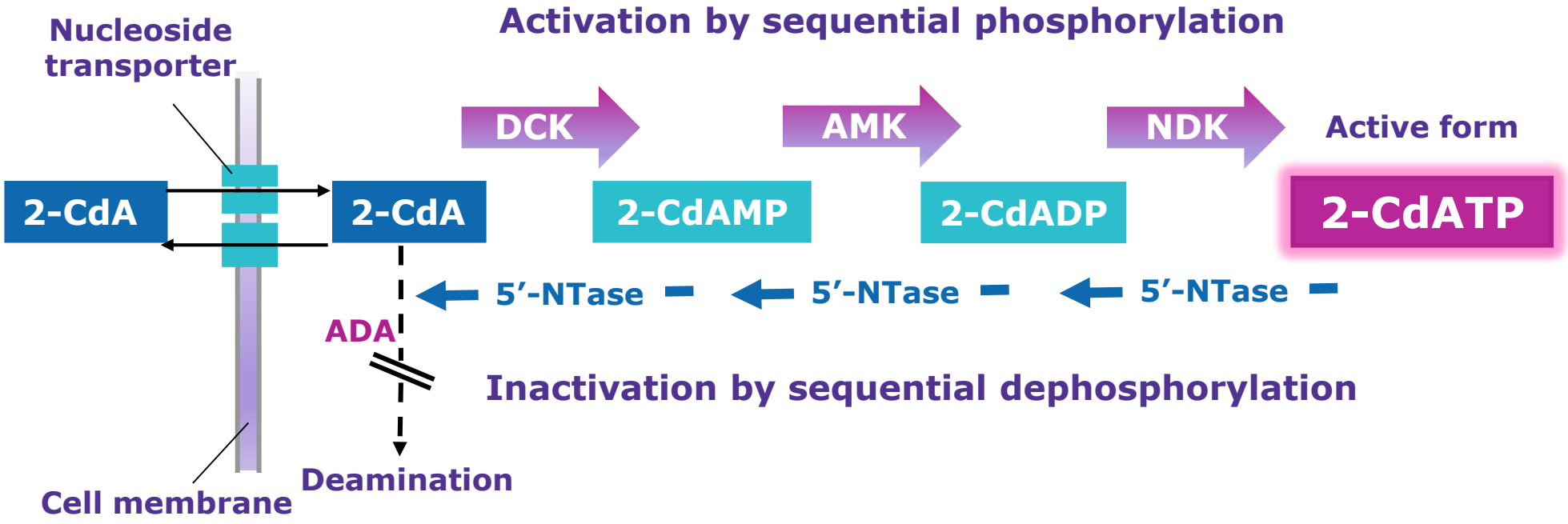
Cladribine (2Cd-ATP) differs from deoxyadenosine, one of the building blocks of DNA, by a chlorine substitution for hydrogen[1,2]



2-chlorodeoxyadenosine (cladribine)[3]

1. Carson DA *et al. Proc Natl Acad Sci USA* 1980;77:6865-9. **2.** Beutler E. *Lancet* 1992;340:952-6. 3**.** Sigal DS *et al. Blood* 2010;116:2884–96.

Proposed activation mechanism of cladribine



- Accumulation of cladribine deoxynucleotides is toxic to cells[5,6]
- Lymphocytes are believed to be particularly susceptible because they have a low ratio of 5'-Ntase to DCK[6,7]

ADA, adenosine deaminase; 2-CdA, 2-chloro-2'-deoxyadenosine; 2-CdADP, 2-chloro-2'-deoxyadenosine diphosphate; 2-CdAMP, 2-chloro-2'-deoxyadenosine monophosphate; 2-CdATP, 2-chloro-2'-deoxyadenosine triphosphate; 5-NTase, 5`nucleotidase; AMK, adenosine monophosphate kinase; DCK, deoxycytidine kinase; NDK, nucleoside diphosphate kinase.

1. Lotfi K *et al. Leuk Lymphoma* 2003;44:1705–12. **2.** Kawasaki H *et al. Blood* 1993;81:597–601. **3.** Leist TP, Weissert R. *Clin Neuropharmacol* 2011;34:28–35. **4.** Saven A, Piro LD. *Ann Intern Med* 1994;120:784–91. **5.** Carson DA, *et al. Proc Natl Acad Sci USA* 1980;77:6865–9. **6.** Carson DA, *et al. Blood* 1983;62:737–43. **7.** Kawasaki H, *et al. Blood* 1993;81:597–601.

Cladribine tablets: regulatory status

The biopharmaceutical division of Merck KGaA, Darmstadt, Germany announced on July 14, 2016 that the European Medicines Agency (EMA) has accepted for review the Marketing Authorization Application (MAA) of the investigational product Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis (MS) in Europe and Canada. At present, a Letter of Intent has been submitted to the EMA only.

The process forward with other regulatory authorities, including the US Food and Drug Administration (FDA), is under consideration/evaluation. Cladribine tablets has not been established to be safe or effective and has not been approved by the FDA for any indication.

Cladribine Tablets Clinical Trial Program

Study	Status	Patients (n)	Treatment	Primary Endpoint
CLARITY[1] (NCT00213135) • Phase III, randomized, double-blind	Completed	Previously treated, RRMS (1326)	Cladribine tablets 3.5 mg/kg, 5.25 mg/kg, placebo	ARR at Year 2
CLARITY EXT[2] (NCT00641537) • Phase IIIb, randomized, double-blind	Completed	Subjects from CLARITY (867)	Placebo crossover	Safety
ORACLE-MS[3] (NCT00725985) • Phase III, randomized, double-blind	Completed	Treatment-naïve with first clinical demyelinating event (617)	Cladribine tablets 3.5 mg/kg, 5.25 mg/kg, placebo	Time to conversion to clinically definite MS according to Poser
ONWARD[4] (NCT00436826) • Phase II, randomized, double-blind	Completed	RRMS on IFN β therapy (214)	Cladribine tablets 3.5 mg/kg + IFN β, placebo + IFN β	Safety
PREMIERE Registry[5] (NCT01013350) • Observational cohort study	Ongoing	Subjects who participated in cladribine tablets clinical trials	N/A	Safety

1. Giovannoni G *et al. N Engl J Med* 2010;362:416-26. **2.** Giovannoni G *et al*. AAN 2013 [P07.119]. **3.** Leist TP *et al. Lancet Neurol* 2014;13:257–67. **4.** ClinicalTrials.gov. NCT00436826. https://clinicaltrials.gov/show/NCT00436826. **5.** ClinicalTrials.gov. NCT01013350. https://clinicaltrials.gov/show/NCT01013350.

03

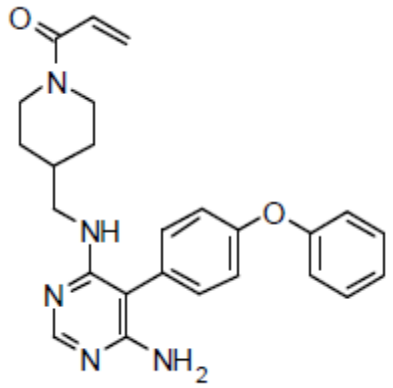
M2951 (MSC2364447C) overview

M2951 Compound Description

- M2951 is an investigational inhibitor of Bruton's tyrosine kinase (BTK), a non-receptor tyrosine kinase involved in signal transduction by the B-cell receptor[1].
  - Blocks the activation of innate immune cells downstream of Fc receptor (FcR) activation

- Based on preclinical data, M2951 is thought to act by irreversibly binding to the ATP binding pocket of BTK with high selectivity

- M2951 is thought to act by inhibiting primary B-cell responses such as proliferation, antibody and cytokine release, and activation without affecting T-cell activation.



1. Hartkamp LM, Radstake TRDJ, Reedquist KA. 18 September 2015;7:27—34

M2951 Clinical Trial Program*

Study	Status	Patients (n)	Treatment	Primary Endpoint
NCT02975349[1] • Phase II, randomized, double-blind, placebo-controlled • Parallel open-label, active-controlled	Not yet recruiting	RRMS (estimated enrollment=250)	M2951 low, mid and high dose; Tecfidera (120 mg BID for 7 days followed by 240 mg BID), placebo	Efficacy, dose-response on Gd^+ T1 MRI lesions

* M2951 is also being investigated in rheumatoid arthritis and systemic lupus erythematosus

1. https://clinicaltrials.gov/show/NCT02975349