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ADISINSIGHT REPORT

Decitabine/Cedazuridine: First Approval

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Abstract
A fixed dose oral combination (FDC) of decitabine and cedazuridine (Inqovi®), is being developed by Astex Pharmaceuticals (a subsidiary of Otsuka Pharmaceuticals) for the treatment of various cancers like myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), acute myeloid leukaemia (AML), glioma and solid tumours. Decitabine, a DNA methyltransferase inhibitor approved for the treatment of MDS and CMML, is degraded by cytidine deaminase in the gastrointestinal tract and liver, thereby limiting oral bioavailability. Cedazuridine is a proprietary, patented cytidine deaminase inhibitor that, when added to decitabine, increases oral bioavailability of the drug. In July 2020, decitabine/cedazuridine received its first approval in the USA and Canada for the treatment of MDS and CMML. In the USA, it is indicated for use in adults with MDS and CMML, including previously treated and untreated, de novo and secondary MDS with the following French–American–British subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts and CMML) and intermediate-1, intermediate-2 and high-risk International Prognostic Scoring System groups. Clinical studies for AML, glioma and solid tumours are underway in several countries worldwide. This article summarizes the milestones in the development of decitabine/cedazuridine leading to this first approval for the treatment of MDS and CMML.

Decitabine/Cedazuridine (Inqovi®): Key points

An oral FDC of decitabine and cedazuridine is being developed by Astex Pharmaceuticals for the treatment of cancers, such as MDS, CMML and AML

Received its first approval on 7 July 2020 in the USA and Canada

Approved for the treatment of adults with MDS and CMML

1 Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of the bone marrow haematopoietic stem cells, characterized by impaired haematopoiesis, peripheral blood cytopenias, increased blast populations in the peripheral blood and/or bone marrow and a higher risk of developing acute myeloid leukaemia (AML) [1, 2]. While allogeneic hematopoietic stem cell transplant is the only potentially curative option for MDS (and other advanced haematological malignancies), many patients are not eligible for the procedure and the hypomethylating agents (HMAs) azacitidine and decitabine are the mainstay of therapy to alleviate cytopenia, control disease and prolong survival in these patients [1, 3–5]. HMAs are cytidine-nucleoside analogues that incorporate into DNA during the S-phase of the cell cycle and covalently bind DNA methyltransferase 1, which is then degraded and depleted within the cell, resulting in reduced methylation of CpG residues in genomic DNA, altered epigenetic pattern and modified gene expression [3, 6].

HMAs are administered parenterally for 5–7 days per 28-day treatment cycle, with multiple treatment cycles necessary to achieve a response [7]. Interruption of therapy in patients that respond to treatment can result in disease

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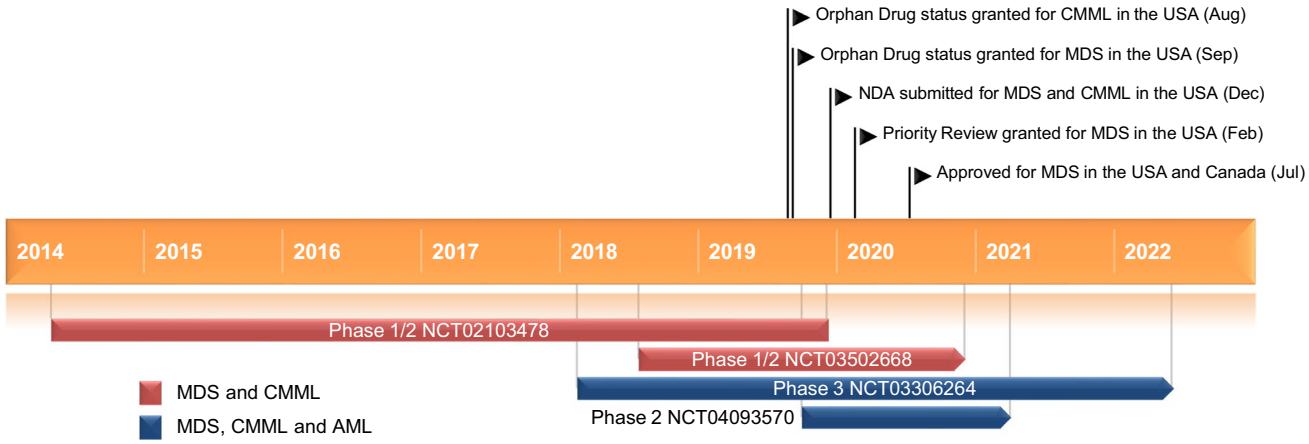


Key milestones in the development of decitabine/cedazuridine. *AML* acute myeloid leukaemia, *CMML* chronic myelomonocytic leukaemia, *MDS* myelodysplastic leukaemia, *NDA* New Drug Application.

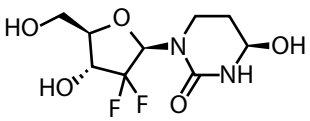
progression. An orally bioavailable HMA could potentially decrease the burden of monthly, multiple-day, intravenous (IV) infusions or subcutaneous injections, particularly for long-term responders who may require treatment for months or years [7]. However, the oral bioavailability of decitabine and azacitidine is limited because of rapid inactivation by cytidine deaminase (CDA), which is highly expressed in the gut and liver [7, 8] and in some solid tumours [6]. Inhibition of CDA offers a strategy to improve the oral bioavailability of HMAs. The competitive CDA inhibitor tetrahydrouridine (THU) increases the oral bioavailability of decitabine. However, THU is unstable in acidic environments, which led to the development of cedazuridine (E7727; Astex Pharmaceuticals), a novel CDA inhibitor designed to overcome the instability of THU and increase the oral bioavailability of decitabine following oral administration [7, 8].

A fixed dose oral combination (FDC) of decitabine and cedazuridine (Inqovi®), is being developed by Astex Pharmaceuticals (a subsidiary of Otsuka Pharmaceuticals) for the treatment of various cancers like myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), acute myeloid leukaemia (AML), glioma and solid tumours. In July 2020, decitabine/cedazuridine received its first approval in the USA [9] and Canada [10] for the treatment of MDS and CMML. In the USA, decitabine/cedazuridine is indicated for use in adults with MDS and CMML, including previously treated and untreated, de novo and secondary MDS/CMML with the following French–American–British (FAB) subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blast, and CMML) and intermediate-1, intermediate-2 and high-risk International Prognostic Scoring System (IPSS) groups [11]. The recommended dosage of decitabine/cedazuridine is one tablet (containing 35 mg decitabine and 100 mg cedazuridine) orally once daily on days 1 through 5 of each 28-day cycle for a minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles. Monitoring and dosage modifications may be required to manage adverse reactions [11]. Clinical studies for AML, glioma and solid tumours are underway in several countries worldwide.

1.1 Company Agreements

In March 2014, Otsuka Pharmaceutical Co Ltd. announced an agreement with Eisai Inc. to acquire the rights for the development and sale of Dacogen® (an IV formulation of decitabine) in the US, Canada and Japan, as well as licensing rights worldwide (excluding Mexico) [12, 13]. Eisai retained the rights in Mexico, and Janssen Pharmaceutical Companies retained its worldwide development and commercialization rights (excluding the USA, Canada, Mexico and Japan). Otsuka also acquired from Eisai Inc. the patent rights to an enzyme inhibitor cedazuridine (E7727), which together with decitabine is being developed as the oral fixed-dose combination decitabine/cedazuridine (ASTX727) [12, 13].

In June 2019, Taiho Pharmaceutical and Astex Pharmaceuticals (an Otsuka subsidiary) entered into a marketing agreement for guadecitabine and ASTX727 in the US and Canada. Commercialization rights for the two drugs were transferred to Taiho Oncology and Taiho Pharma Canada [14].



Chemical structure of cedazuridine

2 Scientific Summary

2.1 Pharmacodynamics

Decitabine induces hypomethylation in vitro and in vivo [11]. In the phase 1 part of a phase 1/2 study (NCT02103478), administration of decitabine 20–40 mg plus cedazuridine 40–100 mg in 43 patients with MDS or CMML resulted in dose-dependent reduction in long interspersed nuclear element-1 (LINE-1) methylation compared to baseline [7]. The greatest average relative demethylation was observed on day 8 [7] and at the end of the treatment cycle, there was less than complete recovery of methylation to baseline levels [11]. In 78 patients who received either oral decitabine 35 mg plus cedazuridine 100 mg or IV decitabine 20 mg/m^2 in the phase 2 part of the study, no clinically or statistically significant difference between oral or IV dosing was seen in the effect on global DNA methylation [8]. The absolute difference in the maximum least-squares mean (LSM) % LINE-1 demethylation (primary endpoint) between oral and IV dosing in cycles 1 and 2 was ≤ 1%, with the 95% CI of the difference containing zero [8]. Similarly, in 133 patients who received oral decitabine/cedazuridine 35/100 mg fixed-dose combination or IV decitabine 20 mg/m^2 in the phase 3 ASCERTAIN study (NCT03306264), there was no significant difference in % LINE-1 DNA demethylation between the two treatment groups in cycles 1 and 2 (< 1% difference in each cycle) [15].

2.2 Pharmacokinetics

Following administration of oral decitabine/cedazuridine at the recommended dosage in 133 patients with MDS or CMML in the phase 3 ASCERTAIN study (NCT03306264), the geometric mean ratio (GMR) of the 5-day cumulative decitabine area under the curve (AUC) (primary endpoint) compared with that of IV decitabine was 99% (90% CI 93–106) [11]. The GMR of decitabine AUC following the first dose of decitabine/cedazuridine compared with that of IV decitabine on day 1 was 60% (90% CI 55–65) and the GMR of decitabine AUC compared with that of IV decitabine on day 5 was 106% (90% CI 98–114) [11].

Features and properties of decitabine/cedazuridine	
Alternative names	ASTX 727; ASTX727 LD; INQOVI®;
Class	Antineoplastics; aza compounds; deoxyribonucleosides; fluorinated hydrocarbons; pyrimidine nucleosides; ribonucleosides; small molecules; triazines
Mechanism of Action	Cedazuridine inhibits cytidine deaminase in the gastrointestinal tract and liver, thereby increasing systemic exposure of decitabine following oral administration
Route of Administration	Oral
Pharmacodynamics	In patients with MDS or CMML, there was no significant difference in LINE-1 DNA demethylation between oral decitabine/cedazuridine and intravenous decitabine
Pharmacokinetics	Oral decitabine/cedazuridine 35/100 mg fixed-dose combination achieved ≈ 99% of decitabine 5-day AUC systemic exposures compared with intravenous decitabine 20 mg/m^2
	C_{max} of decitabine and cedazuridine reached in median of 1 h and 3 h, respectively
	Steady state of decitabine and cedazuridine reached in 2 days
	Mean terminal half-life of decitabine and cedazuridine 1.5 h and 6.7 h, respectively
Most frequent adverse reactions	
Any-grade	Fatigue, constipation, haemorrhage, myalgia, nausea, arthralgia
Grade 3/4	Pneumonia, sepsis
Most frequent grade 3/4 laboratory abnormalities	Decreased leukocytes, decreased platelet count, decreased neutrophil count
ATC codes	
WHO ATC code	A (Alimentary Tract and Metabolism); L01B-C08 (Decitabine
EphMRA ATC code	A (Alimentary Tract and Metabolism); L1B (Antimetabolites)
Chemical Name	4-amino-1-[(2*R*,4*S*,5*R*)-4-hydroxy-5(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2(1*H*)-one

AUC area under the concentration–time curve, C_{max} peak plasma concentration, *CMML* chronic myelomonocytic leukaemia, *LINE-1* long interspersed nuclear element-1, *MDS* myelodysplastic syndrome

Key clinical trials of decitabine/cedazuridine sponsored by Astex Pharmaceuticals, Inc

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Decitabine/cedazuridine, decitabine	MDS, CMML and AML	3	Recruiting	Multinational	ASTX727-02; NCT03306264
Decitabine/cedazuridine	MDS, CMML and AML	2	Enrolling by invitation	USA, Canada	ASTX727-06; NCT04093570
Decitabine/cedazuridine	MDS and CMML	1/2	Completed	USA, Canada	ASTX727-01; NCT02103478
Decitabine/cedazuridine	MDS	1/2	Recruiting	USA	ASTX727-03; NCT03502668

AML acute myeloid leukaemia, *CMML* chronic myelomonocytic leukaemia, *MDS* myelodysplastic syndrome

Following administration of oral decitabine 20–40 mg once daily (0.6 to 1.1 times the recommended dose) in combination with 100 mg oral cedazuridine, an approximately dose-proportional increase in decitabine peak concentrations (C_{max}) and AUC over the dosing interval was observed [11]. Likewise, an approximately dose-proportional increase in cedazuridine C_{max} and AUC over the dosing interval was observed following administration of oral cedazuridine 40–100 mg once daily (0.4 to 1.0 times the recommended dose) in combination with 20 mg oral decitabine [11].

With the recommended dosage of decitabine/cedazuridine for five consecutive days, C_{max} of decitabine was reached in a median of 1 h (range 0.3–3.0 h) and that of cedazuridine was reached in a median of 3 h (range 1.5–6.1 h) [11]. Decitabine and cedazuridine steady state is reached in 2 days. The accumulation ratio of decitabine was 1.7 and that of cedazuridine was 1.1. Oral decitabine exposure was increased with cedazuridine; the bioavailability of cedazuridine was 20%. At steady state, the apparent volume of distribution of decitabine and cedazuridine was 417 L and 296 L, respectively. In vitro, the unbound fraction of decitabine was 96–94% (17–342 ng/mL) and that of cedazuridine was 66–62% (1000–50,000 ng/mL) [9].

Decitabine was primarily metabolized by CDA and by physicochemical degradation, while cedazuridine was converted to epimer by physicochemical degradation [9]. At steady state, the mean terminal half-life of decitabine was 1.5 h and that of cedazuridine was 6.7 h. The apparent clearance of decitabine and cedazuridine was 197 and 30.3 L/h, respectively. In healthy subjects, 46% (21% as unchanged drug) of cedazuridine was excreted in urine and 51% (27% as unchanged drug) was excreted in the faeces [9].

Coadministration of decitabine/cedazuridine with drugs that are metabolized by CDA may result in increased systemic exposure of these drugs and potentially increase their toxicity; therefore, coadministration of decitabine/cedazuridine with drugs that are metabolized by CDA should be avoided [9].

2.3 Therapeutic Trials

2.3.1 Phase 3 Study

Oral decitabine/cedazuridine 100/35 mg fixed-dose tablet demonstrated equivalent decitabine exposure to IV decitabine 20 mg/m^2 when both were administered over 5 days (primary outcome; Sect. 2.2) and showed clinical responses consistent with those seen in patients receiving IV decitabine in the ongoing randomized, cross-over, phase 3 ASCERTAIN study in 133 adults with MDS or CMML (NCT03306264) [11, 15]. Patients included had a median age of 71 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and MDS or CMML, including all FAB classification criteria and IPSS intermediate-1, intermediate- or high-risk prognostic scores. Patients were randomized 1:1 to receive oral decitabine/cedazuridine 100/35 mg on days 1–5 of cycle 1 (28 days) and IV decitabine 20 mg/m^2 on days 1–5 of cycle 2 (28 days) or the reverse sequence. From cycle 3 onwards, all patients received decitabine/cedazuridine 100/35 mg orally once daily on days 1–5 of each 28-day cycle until disease progression or unacceptable toxicity; 20% (27/133) of patients went on to receive stem cell transplantation following decitabine/cedazuridine treatment [11, 15].

After a median follow-up of 12.6 months (median treatment duration 8.2 months), the complete response (CR) rate in patients receiving decitabine/cedazuridine was 21% (95% CI 15–29%), the median duration of CR was 7.5 (range 1.6–17.5) months and the median time to CR was 4.3 (2.1–15.2) months [11]. Of the 57 patients dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 53% ($n=30$) of patients became independent of RBC and platelet transfusions during any 56-day post-baseline period. Among the 76 patients independent of both RBC and platelet transfusions at baseline, 63% ($n=48$) of patients remained independent of transfusions during any 56-day post-baseline period [11].

2.3.2 Phase 1/2 Study

The phase 1 dose-escalation part of an open-label, multicentre, phase 1/2 study (NCT02103478; $n=43$ evaluable) in patients (aged ≥ 18 years) with MDS or CMML determined that oral decitabine 30–40 mg plus cedazuridine 100 mg produced decitabine exposure comparable to IV decitabine 20 mg/m^2 [7]. The percent of 5-day AUC and C_{max} for oral over IV fraction for decitabine 30 mg was 81% and 78%, respectively, and that for decitabine 40 mg was 128% and

90%. A 5-day cycle of the average of decitabine 30 mg and 40 mg doses (i.e. 35 mg) plus cedazuridine 100 mg was selected for further evaluation in the phase 2 part of the study [7].

The open-label, randomized, cross-over, phase 2 part of the study (NCT02103478) determined that oral decitabine 35/100 mg produced consistent efficacy and similar systemic decitabine exposure to that of IV decitabine 20 mg/m^2 [8, 11]. Patients ($n = 80$) with MDS or CMML were randomized 1:1 to receive decitabine 35 mg plus cedazuridine 100 mg cedazuridine orally on day 1–5 of cycle 1 (28 days) and decitabine 20 mg/m^2 IV in cycle 2 (28 days) or the reverse sequence. Starting from cycle 3, all patients received oral decitabine/cedazuridine once daily on days 1–5 of each 28-day cycle until disease progression or unacceptable toxicity. Patients initially received the two oral drugs concomitantly as separate capsules in the dose-confirmation stage ($n = 50$) and then as a fixed-dose combination ($n = 30$). The oral over IV geometric LSM ratio of 5-day decitabine AUC was 93.5% (80% CI 82.1–106.5) for the dose-confirmation stage and 97.6% (80% CI 80.5–118.3) for the fixed-dose combination stage (primary endpoint) [8, 11]. After a median follow-up of 24 months (median treatment duration 6.6 months), the CR rate in patients receiving decitabine/cedazuridine was 18% (95% CI 10–28), the median duration of CR was 8.7 (range 1.1–18.2) months and the median time to CR was 4.8 (range 1.7–10.0) months (primary endpoint was assessment of clinical responses). Of the 41 patients dependent on RBC and/or platelet transfusions at baseline, 49% ($n = 20$) of patients became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Among 39 patients who were independent of RBC and platelet transfusions at baseline, 64% ($n = 25$) of patients remained independent of transfusions during any consecutive 56-day post-baseline period [11].

2.4 Adverse Events

The tolerability profile of oral decitabine/cedazuridine was consistent with that of IV decitabine according to pooled data from the phase 3 (NCT03306264) and the phase 2 part of the phase 1/2 study (NCT02103478) [11]. Patients received oral decitabine/cedazuridine 35/100 mg ($n = 106$) or IV decitabine ($n = 107$) in cycles 1 and 2 of the cross-over phases of the two studies, followed by oral decitabine/cedazuridine 35/100 mg ($n = 208$) from cycle 3 onwards. Of the patients who received decitabine/cedazuridine, 61% of patients were exposed to the combination for ≥ 6 months and 24% were exposed for > 1 year [11].

In cycle 1, the most common any-grade adverse reactions (incidence > 20%) with decitabine/cedazuridine were fatigue (29% vs 25% with decitabine), nausea (25% vs 16%), haemorrhage (24% vs 17%) and headache (22% vs 13%) [11]. During this period, the most common (incidence > 5%) grade 3/4 adverse reactions with decitabine/cedazuridine were febrile neutropenia (10% vs 13% with decitabine) and pneumonia (7% vs 5%). The most common (incidence ≥ 40%) any-grade adverse reactions with decitabine/cedazuridine across all treatment cycles were fatigue (55%), constipation (44%), haemorrhage (43%), myalgia (42%), nausea (40%) and arthralgia (40%). The most common (incidence > 10%) grade 3/4 adverse reactions across all cycles were pneumonia (15%) and sepsis (11%). Clinically relevant adverse reactions in < 10% of decitabine/cedazuridine recipients were acute febrile neutrophilic dermatosis (Sweet's syndrome) (1%) and tumour lysis syndrome (0.5%) [11].

In terms of laboratory abnormalities, in cycle 1, the most common adverse reactions (incidence ≥ 60% in either group) with decitabine/cedazuridine and decitabine were decreased leukocytes (any-grade 79% vs 77%; grade 3/4 65% vs 59%), decreased platelet count (any-grade 79% vs 77%; grade 3/4 65% vs 67%) and decreased neutrophil count (any-grade 70% vs 62%; grade 3/4 65% vs 59%) [11]. Across all treatment cycles, the most common (incidence > 70%) laboratory abnormalities with decitabine/cedazuridine were decreased leukocytes (any-grade 87%; grade 3/4 81%), decreased platelet count (any-grade 82%; grade 3/4 76%), decreased neutrophil count (any-grade 73%; grade 3/4 71%) and decreased haemoglobin (any-grade 71%) [11].

Serious adverse reactions were reported in 68% of decitabine/cedazuridine recipients, with febrile neutropenia (30%), pneumonia (14%) and sepsis (13%) among the most common (incidence > 5%) serious adverse reactions [11]. Fatal adverse reactions occurred in 6% of patients, including sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and cerebral haemorrhage and sudden death (one case each). Adverse reactions resulted in permanent discontinuation of treatment in 5% of patients receiving decitabine/cedazuridine, with the most common reasons for treatment discontinuation being febrile neutropenia (1%) and pneumonia (1%). Of the patients receiving decitabine/cedazuridine, 41% required dose interruptions because of adverse reactions, with neutropenia (18%), febrile neutropenia (8%), thrombocytopenia (6%) and anaemia (5%) among the most common reasons. Dose reductions due to adverse reactions occurred in 19% of patients who received decitabine/cedazuridine, with the most common (incidence > 2%) reasons including neutropenia (12%), anaemia (3%) and thrombocytopenia (3%) [11].

IV decitabine has been associated with differentiation syndrome and interstitial lung disease during post-marketing experience [11].

2.5 Ongoing Clinical Trials

In addition to the ongoing phase 3 study in patients with MDS or CMML (NCT03306264), which has been expanded to include an AML arm in the EU, a phase 2 extension study is enrolling patients who participated in previous decitabine/cedazuridine trials. The study will assess the safety of decitabine/cedazuridine and the survival status of patients receiving the combination longer term. Also recruiting patients is an open-label, multicentre phase 1/2 study (NCT03502668) that will assess the safety, pharmacodynamics and pharmacokinetics of, and hematologic responses with, various low doses and schedules of decitabine/cedazuridine in subjects with IPSS low-risk or intermediate-1 MDS. The study plans to enrol ≈ 160 patients. The primary outcomes of the study will be the incidence of drug-related grade ≥ 3 adverse events or dose-limiting toxicities (if any) for each cohort dose/schedule (phase 1) and haematological responses in each cohort (phase 2).

3 Current Status

On 7 July 2020, decitabine/cedazuridine received its first approval in the USA [9] and Canada [10] for the treatment of MDS and CMML. In the USA, it is indicated for use in adults with MDS and CMML, including previously treated and untreated, de novo and secondary MDS/CMML with the following French–American–British subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts, and CMML) and intermediate-1, intermediate-2 and high-risk IPSS groups [11].

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Declarations

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Ethics approval, Consent to participate and consent for publication, Availability of data and material, Code availability Not applicable.

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