NEW LONG-TERM DATA:
~4 YEAR DATA vs BR IN 1L[1]
~3 YEAR DATA vs IBRUTINIB IN 2L[2]

1L=first line; 2L=second line; BR=bendamustine+rituximab; CLL=chronic lymphocytic leukemia.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage, including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.

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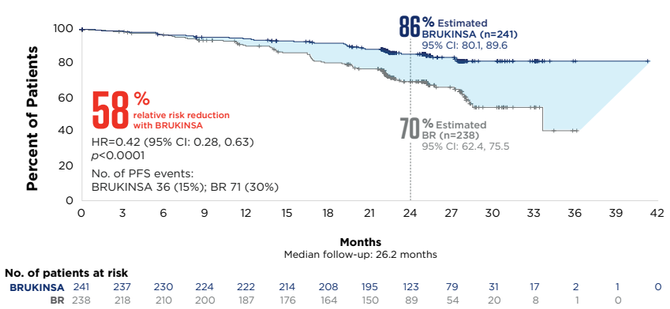
BRUKINSA DELIVERS POWERFUL EFFICACY IN PATIENTS WITHOUT AND WITH DEL(17p)[3,4]

Initial Analysis (26 months in Cohort 1, 31 months in Cohort 2)

Superior PFS vs BR: patients without del(17p)[3,4]

(Cohort 1: primary endpoint)

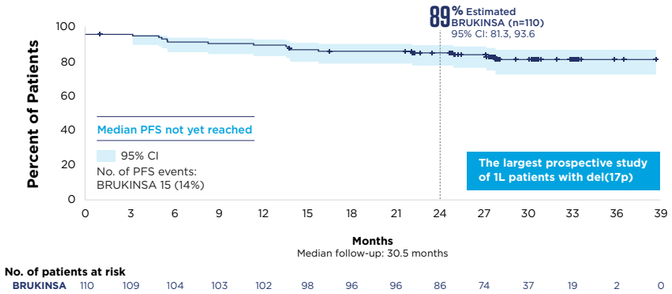


No. of patients at risk														
BRUKINSA	241	237	230	224	222	214	208	195	123	79	31	17	2	1	0
BR	238	218	210	200	187	176	164	150	89	54	20	8	1	0	

Median PFS was not reached in either arm.[3,4]
Prespecified analysis assessed by IRC.[4]

Consistent PFS in BRUKINSA-only arm: patients with del(17p)[4]

(Cohort 2: secondary endpoint)



No. of patients at risk														
BRUKINSA	110	109	104	103	102	98	96	96	86	74	37	19	2	0

Prespecified analysis assessed by IRC.[4]

SEQUOIA was a global Phase 3, randomized, open-label, multicenter trial evaluating BRUKINSA vs BR in 479 patients with previously untreated CLL/SLL without del(17p). 110 patients with del(17p) were evaluated in separate single-arm cohort and received BRUKINSA only. The primary endpoint was PFS per IRC in the ITT population in the BRUKINSA arm and the BR arm, with minimum 2-sided alpha of 0.05 for superiority.[3,4]

CI=confidence interval; HR=hazard ratio; IRC=independent review committee; ITT=intent to treat; PFS=progression-free survival; SLL=small lymphocytic lymphoma.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

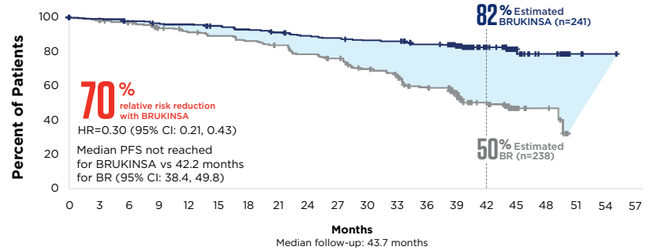
Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

CONSISTENT BENEFIT SUSTAINED OVER ~4 YEARS*[1]

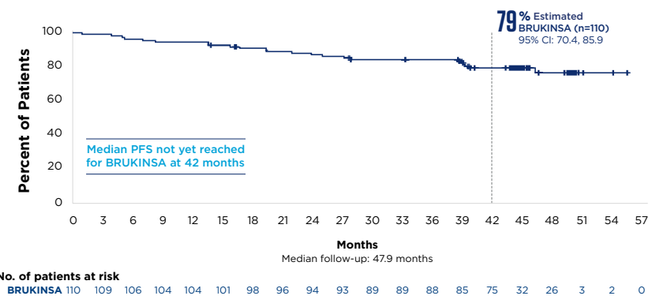
Long-Term Analysis (~4 years)

PFS vs BR: patients without del(17p)[1]



No. of patients at risk																			
BRUKINSA	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0
BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		

PFS in BRUKINSA-only arm: patients with del(17p)[1]



No. of patients at risk																			
BRUKINSA	110	109	106	104	104	101	98	96	94	93	89	89	88	85	75	32	26	3	2	0

*Exploratory analyses.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Infections (continued)

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

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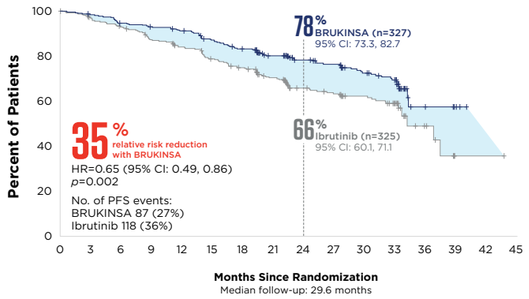
BRUKINSA DELIVERS POWERFUL EFFICACY IN PATIENTS WITHOUT AND WITH DEL(17p)[5]

Initial Analyses (30 months for PFS, 25 months for ORR)

Superior PFS: all-comer population[5]

(secondary endpoint)



No. of patients at risk

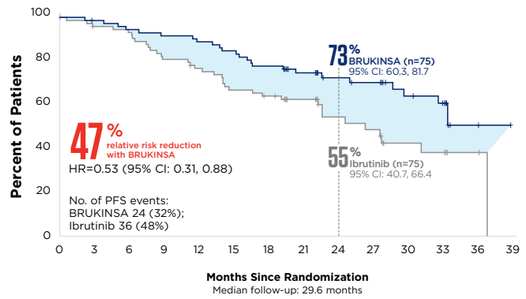
BRUKINSA	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

Data presented are consistent with label.[6]

Prespecified analysis assessed by both IRC and investigator with similar results. Median PFS has not yet been reached with BRUKINSA vs 34 months with ibrutinib.[5]

PFS: patients with del(17p)[5]

(secondary endpoint)



No. of patients at risk

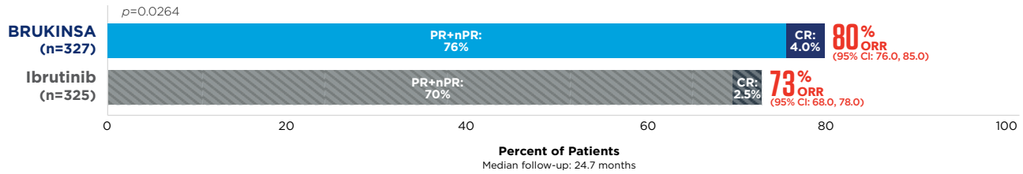
BRUKINSA	75	71	68	66	64	61	56	47	32	30	21	18	3	0
Ibrutinib	75	70	68	59	55	48	45	34	19	17	10	9	2	0

Data presented are consistent with label.[6]

All subgroup analyses are exploratory and descriptive in nature. Assessed by both IRC and investigator with similar results.[5]

Superior ORR: all-comer population[3]

(primary endpoint)



Assessed by both IRC and investigator with similar results.[5]

ALPINE was a global Phase 3, randomized, open-label, multicenter trial evaluating BRUKINSA vs ibrutinib in 652 patients with relapsed/refractory CLL/SLL who received ≥1 prior systemic therapy. Statistical analysis for PFS and ORR were initially conducted for noninferiority. When noninferiority was met, superiority was tested.[3,5]

CR=complete response; nPR=nodular partial response; ORR=overall response rate; PR=partial response.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

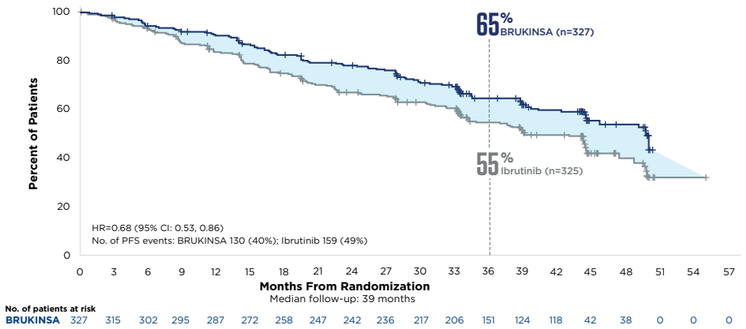
Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

CONSISTENT PFS vs IBRUTINIB SUSTAINED OVER 3 YEARS*[2]

Long-Term Analysis (~3 years)

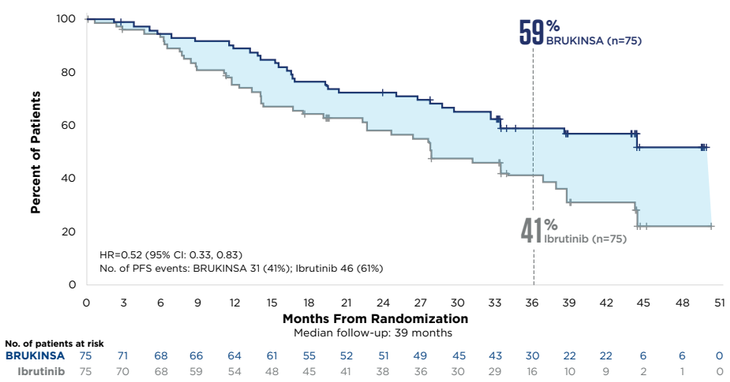
PFS: all-comer population[2]



No. of patients at risk

BRUKINSA	327	315	302	295	287	272	258	247	242	236	217	206	151	124	118	42	38	0	0	0
Ibrutinib	325	305	293	273	258	242	229	212	200	194	182	171	116	92	88	28	22	1	1	0

PFS: patients with del(17p)[2]



No. of patients at risk

BRUKINSA	75	71	68	66	64	61	55	52	51	49	45	43	30	22	22	6	6	0
Ibrutinib	75	70	68	59	54	48	45	41	38	36	30	29	16	10	9	2	1	0

*Exploratory analyses.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

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1L: SEQUOIA

Initial Analysis: Low rates of afib/flutter in patients without or with del(17p)[4]

Cohort 1: without del(17p)

3.3% BRUKINSA (n=240) vs **2.6%** BR (n=227)

Cohort 2: with del(17p)

4.5% BRUKINSA (n=111)

All subgroup analyses are exploratory and descriptive in nature.
Prespecified analyses assessed by IRC.

ARs in patients without del(17p) were consistent with the established safety profile of BRUKINSA[3,7]

Adverse Reactions	ARs in ≥10% of Patients Without Del(17p)				Pooled Safety Population*	
	BRUKINSA (n=240)		BR (n=227)		BRUKINSA (N=1550)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Musculoskeletal pain	33	2	17	0.4	30	2
Upper respiratory tract infection	28	1	15	0.9	39	2
Pneumonia	13†	5	8‡	4	20	11
Hemorrhage	27†	4	4	0.4	30	4
Hypertension	14	7	5	3	14	7
Rash	24	1	30	5	28	0.9
Bruising	24	0	3	0	23	0.1
Cough	15	0	10	0	19	0.1
Diarrhea	14	0.8	12‡	0.9	19	2
Constipation	10	0.4	18	0	13	0.3
Nausea	10	0	33	1	11	0.2
Fatigue	14	1	21	2	17	1
Second primary malignancy	13†	6	1	0.4	13	6
Headache	12	0	8	0	11	0.4
Dizziness	11	0.8	5	0	11	0.3

*Includes chronic lymphocytic leukemia, Waldenström's macroglobulinemia, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, and Richter's transformation.[7]
†Includes 3 fatal outcomes.[3]
‡Includes 2 fatal outcomes.[3]

There were no new safety signals at ~4 years with BRUKINSA[1]

AEs=adverse events; afib=atrial fibrillation; ARs=adverse reactions; COVID-19=coronavirus disease 2019.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

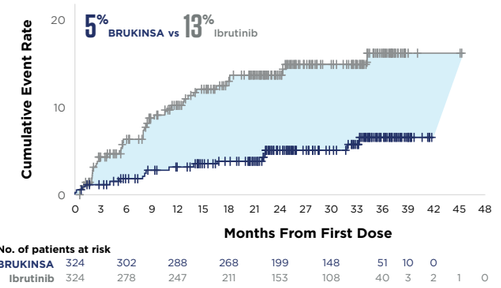
In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

2L: ALPINE

Initial Analysis: Lower rates of cardiac events including afib/flutter and no cardiac deaths vs ibrutinib[2,5]

Atrial fibrillation/flutter[4]

(prespecified analysis)



	BRUKINSA (n=324)	Ibrutinib (n=324)
Cardiac adverse events	69 (21.3%)	96 (29.6%)
Serious cardiac adverse events	6 (1.9%)	25 (7.7%)
Cardiac adverse events leading to treatment discontinuation§	1 (0.3%)	14 (4.3%)
Fatal cardiac events	0 (0%)	6 (1.9%)

§BRUKINSA cardiac-related discontinuation in 1 patient was for ventricular extrasystoles. Ibrutinib cardiac-related discontinuations were for atrial fibrillation (5), cardiac arrest (2), cardiac failure (2), cardiac failure acute (1), congestive cardiomyopathy (1), myocardial infarction (1), palpitations (1), and ventricular fibrillation (1).[2,5]

Assessed by both IRC and investigator with similar results.

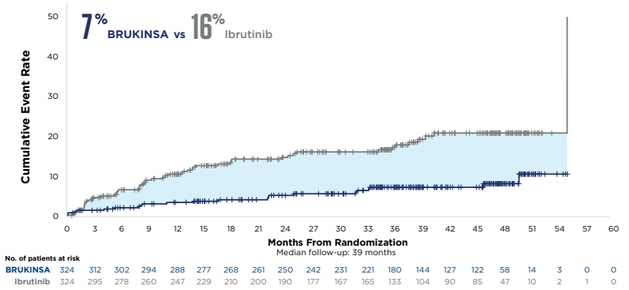
Adverse reactions reported in ≥10% of patients (BRUKINSA vs ibrutinib, respectively) in the ALPINE trial included: upper respiratory tract infection (27% vs 22%), pneumonia (18%¶ vs 19%#), COVID-19 (14%¶ vs 10%#), musculoskeletal pain (26% vs 28%), hemorrhage (24%¶ vs 26%#), hypertension (19% vs 20%), rash (20% vs 21%), bruising (16% vs 14%), diarrhea (14% vs 22%), fatigue (13% vs 14%), cough (11% vs 11%), and dizziness (10% vs 7%).[3]

¶Includes fatal outcomes: pneumonia (9 patients), COVID-19 (8 patients), and hemorrhage (1 patient).[3]
#Includes fatal outcomes: pneumonia (10 patients), COVID-19 (9 patients), and hemorrhage (2 patients).[3]

Continued lower rates of cardiac disorders vs ibrutinib in the 3-year analysis[2]

Atrial fibrillation/flutter[2]

(prespecified analysis)



	BRUKINSA (n=324)	Ibrutinib (n=324)
Cardiac AEs (any grade)	25%	35%
Serious cardiac AEs	3%	10%
Cardiac AEs leading to treatment discontinuation**	0.9%	5%
Cardiac deaths	0%	2%

**Cardiac AEs leading to treatment discontinuation included ventricular extrasystoles, atrial fibrillation/flutter, and cardiac failure for BRUKINSA and atrial fibrillation/flutter, cardiac arrest, cardiac failure, cardiac failure acute, congestive cardiomyopathy, myocardial infarction, palpitations, and ventricular fibrillation for ibrutinib.[2]

IMPORTANT SAFETY INFORMATION (continued)
DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

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IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

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CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

Please see accompanying full Prescribing Information, including Patient Information.

References: 1. Munir T, Shadman M, Robak T, et al. Zanubrutinib (zanu) vs bendamustine + rituximab (BR) in patients (pts) with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): extended follow-up of the SEQUOIA study. Poster presented at: European Hematology Association (EHA) 2023 Hybrid Congress; June 8-15, 2023. Abstract P639. **2.** Brown JR, Eichhorst B, Lamanna N, et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: American Society of Hematology (ASH) Annual Meeting and Exposition; December 9-12, 2023. **3.** BRUKINSA. Package insert. BeiGene USA, Inc; 2023. **4.** Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2022;23(8):1031-1043. **5.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2023;388(4):319-332. **6.** *Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers: Guidance for Industry.* US Department of Health and Human Services, Food and Drug Administration; 2018. Accessed December 20, 2022. https://www.fda.gov/media/102575/download **7.** Data on file. BeiGene USA, Inc.

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