Common Drug Review
Pharmacoeconomic Review Report

September 2017

Drug	certolizumab pegol (Cimzia) (subcutaneous injection)
Indication	Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy
Listing request	As per indication
Manufacturer	UCB Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
DMARD	disease-modifying antirheumatic drug
CDR	CADTH Common Drug Review
CZP	certolizumab pegol
MTC	mixed treatment comparison
nr-axSpA	non-radiographic-axSpA
SC	subcutaneous
SEB	subsequent entry biologic
SF-36	Short-form 36-item Health Survey
TNF	tumour necrosis factor

SUMMARY

Background

Certolizumab pegol (Cimzia; CZP) is a tumour necrosis factor (TNF) alpha-inhibitor, indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy. CZP is available as a 200 mg/mL prefilled syringe. The recommended loading dose of CZP is 400 mg at weeks 0, 2, and 4 followed by a maintenance dose of either 200 mg every two weeks (Q2W), or 400 mg every four weeks (Q4W).[1] The manufacturer submitted CZP for review at the currently marketed price of $664.51 per 200 mg/mL prefilled syringe, which equates to a cost of $19,271 in year 1 and $17,277 in subsequent years.[2] The manufacturer is requesting reimbursement of CZP as per the Health Canada-approved indication.

First-line treatment for AS is widely considered to be nonsteroidal anti-inflammatory drugs (NSAIDs),[3,4] and thus has been used as a proxy for conventional therapy. There are currently four other biologic disease-modifying antirheumatic drugs (DMARDs) indicated in Canada to treat patients with AS who have had an inadequate response to a reasonable trial of conventional therapy: adalimumab, etanercept, golimumab, and infliximab.

CZP has already been reviewed by CADTH Common Drug Review (CDR) for adult patients with moderately to severely active rheumatoid arthritis where the Canadian Expert Drug Advisory Committee (CEDAC) recommended that CZP not be listed, given the limited quality of the trials and the other therapeutic options available.[5] At the time of this review, CZP was also being reviewed by CDR for reducing signs and symptoms and inhibiting the progression of psoriatic arthritis.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer conducted a cost-minimization analysis over a three-year time frame comparing CZP with the four biologic DMARDs (adalimumab, etanercept, golimumab, and infliximab) currently available for reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy. As no head-to-head trials were available comparing CZP to the comparator biologic DMARDs, [redacted] based on a manufacturer-funded mixed treatment comparison (MTC).[6] The outcomes assessed in the MTC were: [redacted].[6]

The manufacturer's base-case analysis was conducted from the Canadian public payer perspective. Only drug acquisition costs were considered (not including mark-up). The average patient weight was assumed to be 80 kg. No direct costs related to infusions were included. The manufacturer also provided an analysis from a societal perspective that included indirect costs associated with lost-time attributable to infusions. A compliance rate of 100% was assumed for all treatments, and no dropout rate was included. The manufacturer stated that unit drug prices were obtained from the Ontario Drug Benefit Formulary (ODBF) Expanded Access Program (EAP) (April 2014). Four one-way sensitivity analyses were undertaken based on compliance rates, dropout rates, discount rates, and mark-ups.

Key Limitations

Few limitations were identified with the economic submission:

- **Use of a three-year time horizon:** The manufacturer's three-year time horizon in the base-case analysis is arbitrary. While varied compliance and dropout rates were provided in sensitivity analyses, the manufacturer did not look at the time at which patients drop out or discontinue treatment with CZP. If a 30% discontinuation rate is applied to all biologic DMARDs after year 1, and a further 10% after each subsequent year, the discounted cost savings with CZP during a three-year period are lower than originally reported ($136 to $30,937 versus $760 to $39,065 as originally reported by the manufacturer). Further, if a one-year time horizon is considered, CZP is more costly than golimumab and adalimumab (Results/Conclusions section).
- **Limitations with the MTC:** The critical appraisal of the MTC within the CDR Clinical Review (Appendix 7) identified the following limitations:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Issues for Consideration

- **Availability of biosimilar infliximab and list price of etanercept:** Although not currently listed by public drug plans, a subsequent entry biologic (SEB) infliximab received a positive listing Canadian Drug Expert Committee (CDEC) recommendation in November 2014 and has a lower price ($650.00 per 100 mg vial) than the branded infliximab.[7] The inclusion of SEB infliximab on public drug formularies may result in CZP being more costly compared with SEB infliximab. These results are explored in the following two bullet points. It should be noted that the price of etanercept increased on the ODB Formulary between the date at which the manufacturer submitted the analysis and the time of CDR review.
- **Weight-based dosing:** Only infliximab (branded and SEB) requires weight-based dosing. In patients weighing 60 kg or less, CZP is more costly than SEB infliximab ($3,671 for year 1, $4,602 for subsequent years).
- **Infliximab dosing:** Three plans (British Columbia, Ontario, and Newfoundland and Labrador) indicate that lower doses of infliximab may be used (3 mg/kg; 3 mg/kg to 5 mg/kg; up to 5 mg/kg) in patients with AS.[8-10] Assuming a patient requires three vials (i.e., weighs between 67 kg and 80 kg), CZP will be more costly than SEB infliximab dosed at 3 mg/kg every eight weeks ($3, 671 for year 1, $4,602 for subsequent years), but still be cost saving compared with branded infliximab ($4,430 in year 1 and $1,980 in subsequent years).
- **Price reduction:** CDR calculated that based on year 1 costs, the price of CZP would need to be reduced by 5.6% (i.e., unit cost of $629) in order to be cost neutral compared with the lowest priced biologic DMARD (golimumab subcutaneous [SC]).

Results/Conclusions

CADTH Common Drug Review critical appraisal of the manufacturer's MTC indicated that at 12 weeks to 16 weeks, the efficacy of CZP is not statistically significantly different from etanercept, adalimumab, or golimumab in terms of ASAS 20, ASAS 40, BASDAI, BASFI, and SF-36, but is statistically significantly lower than infliximab in terms of ASAS 20, BASDAI, and BASFI. [redacted] CDR considered the yearly costs of CZP and comparators.

At the current price, for a patient weight ranging from 61 kg to 80 kg, CZP is more costly than golimumab (+$1,028) and adalimumab (+$21), but is less costly than etanercept (–$1,048), branded infliximab (–$20,231 to –$12,331), and SEB infliximab (–$6,729 to –$1,529) in the first year of treatment, based on published prices. In subsequent years, CZP may be less costly than comparative treatments (savings ranging from $965 to $10,374), with the exception of SEB infliximab (where patients receive three vials or less per dose every eight weeks, an incremental cost between $377 and $4,602).

Cost comparison table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

Existing Product Listing Agreements are not reflected in the table and as such the costs presented in the table may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUG TREATMENTS FOR PATIENTS WITH ANKYLOSING SPONDYLITIS

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Annual Drug Cost ($)
Certolizumab pegol (Cimzia)	**200 mg**	**Single-use prefilled syringe**	**664.5100**	**Year 1: 400 mg at weeks 0, 2, and 4 then 200 mg Q2W or 400 mg Q4W**	**Year 1: 19,271 Thereafter: 17,277**
Biologic DMARDs					
Golimumab SC (Simponi)	50 mg	Prefilled syringe or auto-injector	1520.2100	50 mg monthly	18,243
Adalimumab (Humira)	40 mg	Prefilled syringe or prefilled pen	740.3600	40 mg every other week	19,249
Etanercept (Enbrel)	25 mg	Vial	195.3125	50 mg weekly (one 50 mg dose or 25 mg doses administered every 3 or 4 days)	20,313
	50 mg	Prefilled syringe	390.7425		20,319
Infliximab[a] (Remicade)	100 mg/vial	Vial	987.5600	5 mg/kg[b] initial dose followed by additional 5 mg/kg[b] doses at 2 weeks and 6 weeks after the first infusion, then every 6 weeks to 8 weeks thereafter.	5 mg/kg at weeks 0, 2 and 6 then every 8 weeks[c] Year 1: 31,602 Thereafter: 25,677 5 mg/kg at weeks 0, 2, and 6 then every 6 weeks[d] Year 1: 39,502 Thereafter: 35,552
Infliximab biosimilar[a] (Inflectra)	100 mg/vial	Vial	650.0000[e]	5 mg/kg[b] initial dose followed by additional 5 mg/kg[b] doses at 2 weeks and 6 weeks after the first infusion, then every 6 weeks to 8 weeks thereafter.	5 mg/kg at weeks 0, 2 and 6 then every 8 weeks[c] Year 1: 20,800 Thereafter: 16,900 5 mg/kg at weeks 0, 2 and 6 then every 6 weeks[d] Year 1: 26,000 Thereafter: 23,400

DMARDs = disease-modifying antirheumatic drugs; EAP = Exceptional Access Plan; Q2W = every two weeks; Q4W = every four weeks; ODB = Ontario Drug Benefit; SC = subcutaneous.

[a] Yearly drug costs were based on patients within the weight range of 61 kg to 80 kg.

[b] Some provinces indicate a dose lower than 5 mg/kg may or should be used for infliximab in AS patients (British Columbia, Ontario, Newfoundland and Labrador).[8-10]

[c] Average of 8 doses for the first year and 6.5 doses per year thereafter.

[d] Average of 10 doses for the first year and 9 doses per year thereafter.

[e] Inflectra CDEC Recommendation report, November 2014.[7]

Source: ODB and ODB Formulary EAP (accessed December 2014) unless otherwise indicated.

APPENDIX 1: PRICE REDUCTION ANALYSIS

CADTH Common Drug Review (CDR) calculated the price reduction that would be required to be cost neutral compared with the lowest priced biologic disease-modifying antirheumatic drug (DMARD) in year 1 (golimumab subcutaneous [SC]). As shown in Table 2, the price of CZP would need to be reduced by 5.6% for the cost to be equivalent to golimumab SC in year 1, which would lead to a savings of approximately $21,259 against the most expensive biologic DMARD in year 1 (branded infliximab).

TABLE 2: CADTH COMMON DRUG REVIEW ANALYSIS FOR THREE DIFFERENT PRICE REDUCTION SCENARIOS FOR CERTOLIZUMAB PEGOL

Scenario	Current Price	Year 1 Cost	Reduction Needed	Reduced Price	Savings[a] (Min. to Max.)
Price reduction needed to equal least expensive biologic DMARD	$664.51	$19,271	5.6%	$629.05	–$21,259 to $0

DMARD = disease-modifying antirheumatic drug; max. = maximum; min. = minimum.
[a] Savings compared with all biologic DMARDs, in year 1.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Certolizumab pegol (CZP; Cimzia) 200 mg/mL prefilled syringe
Treatment	CZP 400 mg loading dose at weeks 0, 2, and 4; then 200 mg Q2W or 400 mg Q4W
Comparators	• Adalimumab (Humira) 40 mg every other week • Etanercept (Enbrel) 50 mg every week • Golimumab (Simponi) 50 mg once a month (same date each month) • Infliximab (Remicade) 5 mg/kg given at weeks 0, 2, and 6, then 5 mg/kg every 6 to 8 weeks thereafter[a]
Study Question	From the Ministry of Health and societal perspectives, what is the cost of CZP relative to alternative TNF-alpha inhibitors in the treatment of adult patients with active AS who have had an inadequate response to conventional therapy?
Type of Economic Evaluation	Cost comparison (cost-minimization analysis)
Target Population	Patients representative of the following baseline characteristics: • Age ≥ 18 years • Adult onset active axSpA for at least 3 months • Active disease as defined by the BASDAI ≥ 4, spinal pain ≥ 4 on a 0 to 10 NRS, increased CRP or current evidence of sacroiliitis on MRI • Intolerance to or inadequate response to at least one NSAID • Not exposed to more than one anti-TNF-alpha drug prior to the baseline visit, primary failure to any anti-TNF-alpha therapy (defined as no response within the first 12 weeks of treatment with the anti-TNF-alpha), or exposure to more than 2 previous biologic drugs for axSpA.
Perspective	• Public-payer perspective • Societal perspective
Primary Outcomes Considered	• ASAS 20 response at week 12 (axSpA population) • ASAS 20 response at week 12 (AS population)
Other Outcomes Considered	• Bath Ankylosing Spondylitis indices (i.e., change in BASDAI, change in BASFI, BASDAI 50 response rate) • Patient-reported outcomes (i.e., changes in PtGADA, SF-36, nocturnal back pain, and fatigue)
Key Data Sources	
Cost	ODB EAP (April 2014)
Clinical Efficacy	Manufacturer-submitted MTC, including the sole RCT of CZP in AS (AS001)
Harms	Not reported
Time Horizon	Three years
Results for Base Case	From the public-payer perspective, during a three-year time horizon, the total cost of CZP is expected to be $51,277, which is less than the cost of alternatives: • Range in total costs of alternatives: $52,037 to $90,342 • Range in incremental savings: $760 to $39,065

AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis International Society; axSpA = axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Activity Index; BASDAI 50 = Bath Ankylosing Spondylitis Activity Index 50% improvement; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein; CZP = certolizumab pegol; EAP = Expanded Access Program; mg = milligram; MRI = magnetic resonance imaging; MTC = mixed treatment comparison; NSAID = nonsteroidal anti-inflammatory drug; ODB = Ontario Drug Benefit; PtGADA = Patient's Global Assessment of Disease Activity; Q2W = every two weeks; Q4W = every four weeks; RCT = randomized controlled trial; SF-36 = Short-form 36-item Health Survey.

[a] Some provinces indicate a dose lower than 5 mg/kg may or should be used for infliximab in AS patients (British Columbia, Ontario, Newfoundland and Labrador).[8-10]

Source: Manufacturer's Pharmacoeconomic Submission,[2] manufacturer's mixed treatment comparison.[6]

Manufacturer's results

The manufacturer reported that using CZP at the current market and proposed drug benefit price, relative to alternative anti-TNFs, would result in cost savings to CDR-participating drug plans. The unit cost of CZP was $664.51; which may differ from other anti-TNF treatments given the differential dosing regimens. The cost and number of doses per year are reported in Table 4.

TABLE 4: DRUG UNIT COSTS AND DOSES PER YEAR FOR EACH PRODUCT IN THE BASE CASE

Drug Product	Unit	Unit Price	Average Number of Doses (Year 1)	Average Number of Doses (Year 2)	Average Number of Doses (Year 3)
Certolizumab pegol (CZP)	200 mg	$664.5100	29	26	26
Adalimumab	40 mg	$740.3600	26	26	26
Etanercept	50 mg	$388.6050	52	52	52
Golimumab	50 mg	$1,520.2100	12	12	12
Infliximab[a]	100 mg	$987.5600	36	28	32

CZP = certolizumab pegol.
[a] Assumed an average weight of 80 kg and a maintenance dose every seven weeks.
Source: Manufacturer's Pharmacoeconomic Submission, Table 1.[2]

The manufacturer indicated that from the public payer perspective, CZP at the current market and proposed drug benefit price would result in cost savings relative to alternative anti-TNFs for CDR-participating drug plans (Table 5).

The manufacturer calculated the three-year cost to treat one patient with CZP to be $51,277. The three-year cost for treating one patient with the other anti-TNFs ranged from $52,037 to $90,342.

TABLE 5: MANUFACTURER'S COST-MINIMIZATION ANALYSIS

Drug Product	Three-Year Drug Cost	Incremental Savings With CZP
CZP	$51,276.91	NA
Adalimumab	$54,908.80	$3,631.89
Etanercept	$57,641.78	$6,364.87
Golimumab	$52,036.79	$759.87
Infliximab[a]	$90,341.99	$39,065.07

CZP = certolizumab pegol; NA = not applicable.
[a] Assumed an average weight of 80 kg and a maintenance dose every seven weeks.
Source: Summary of the Manufacturer's Pharmacoeconomic Submission, Table 2.[2]

The manufacturer also reported the results of four one-way sensitivity analyses. These are summarized in Table 6.

TABLE 6: MANUFACTURER'S SENSITIVITY ANALYSIS

Parameter	Original	Revised	Incremental Range in Savings (CZP vs. Comparators)
Base case			$759.87 to $39,065.07
Compliance	100%	80%	$607.90 to $31,252.06
Dropout rates	0% all years	0% year 1, 20% year 2, 50% year 3	$140.90 to $30,629.93
Discount rate	5%	0%	$902.25 to $40,980.45
Mark-up	Not included	8%	$820.66 to $42,190.28

CZP = certolizumab pegol; vs. = versus.
Source: Summary of Manufacturer's Pharmacoeconomic Submission, Table 3, page 22.[2]

CADTH common drug review results

The three-year time horizon submitted by the manufacturer appears to be arbitrary, and given the lack of appropriate long-term comparative effectiveness data, a shorter time horizon may have been more appropriate (one year). Although CDR did not undertake any reanalysis based on the manufacturer's submission, the reviewers refer readers to Table 1 in this document and suggest this as more appropriate to determine the incremental costs and cost savings associated with CZP in year 1 compared with the other indicated and listed biologic DMARDS.

If a longer time horizon is preferred, assuming a discontinuation rate of 30% after year 1 (thus applied to the year 2 cost), and a further 10% every year thereafter (applied to year 3) for all treatments, the resulting cost savings are reduced from the manufacturer's base-case analysis (Table 7). Discontinuation rates were applied for subsequent years.

TABLE 7: CADTH COMMON DRUG REVIEW SENSITIVITY ANALYSIS BASED ON REVISED DISCONTINUATION RATES

Drug Product	Year 1 Cost	Year 2 Cost	Year 3 Cost	Total Cost	Incremental Savings (vs. CZP)
CZP	$19,271	$11,489	$9,356	$40,116	
Adalimumab	$19,249	$12,801	$10,424	$42,474	$2,358
Etanercept[a]	$20,313	$13,512	$11,003	$44,833	$4,717
Golimumab	$18,243	$12,131	$9,878	$40,252	$136
Infliximab (branded)[b,c]	$31,602	$17,075	$13,904	$62,581	$22,465
Infliximab (SEB)[b,c]	$20,800	$11,239	$9,151	$41,190	$1,074

CZP = certolizumab pegol; SEB = subsequent entry biologic; vs. = versus.
[a] The 50 mg dose has been used to compare with CZP.
[b] Administration every eight weeks has been used to compare with CZP.
[c] Assumed an average weight of 80 kg.

Some provinces indicate that physicians should administer infliximab at a dose of 3 mg/kg (British Columbia[8]), while others indicate a dose of up to 5 mg/kg (Ontario[10] and Newfoundland and Labrador[9]). Given that infliximab may be used at a lower dose, and that dosing is weight-based, a sensitivity analysis assessing the comparative cost of CZP and infliximab 3 mg/kg was undertaken (Table 8). Note: this does not take into account any differences in clinical effectiveness that result from a lower dose of infliximab. The results indicate that CZP is still cost saving compared with branded infliximab, but the amount of

cost savings is reduced (range: $1,980 to $10,356). When comparing CZP with SEB infliximab, CZP is more costly than SEB infliximab when the infliximab maintenance dose is every eight weeks ($3,671 to $4,602), and slightly cost saving when the infliximab maintenance dose is every six weeks ($229 to $273).

TABLE 8: CADTH COMMON DRUG REVIEW SENSITIVITY ANALYSIS BASED ON REVISED INFLIXIMAB DOSE

Comparators	Strength	Dose Form	Price ($)	Average Dose	Yearly Drug Cost ($)	Incremental Cost (vs. CZP)
CZP (Cimzia)	**200 mg**	**Single-use prefilled syringe**	**664.5100**	**Year 1: 400 mg at weeks 0, 2, and 4, then 200 mg Q2W or 400 mg Q4W**	**Year 1: 19,271 Thereafter: 17,277**	**NA**
Infliximab[a] (Remicade)	100 mg/vial	Vial	987.5600	3 mg/kg dose at weeks 0, 2, and 6, then every 6 weeks to 8 weeks thereafter	3 mg/kg at weeks 0, 2, and 6 then every 8 weeks[b] Year 1: 23,701 Thereafter: 19,257 3 mg/kg at weeks 0, 2, and 6 then every 6 weeks[c] Year 1: 29,627 Thereafter: 26,664	 $4,430 $1,980 $10,356 $9,387
Infliximab[a] (Inflectra)	100 mg/vial	Vial	650.00	3 mg/kg dose at weeks 0, 2 and 6, then every 6 to 8 weeks thereafter	3 mg/kg at weeks 0, 2, and 6 then every 8 weeks[b] Year 1: 15,600 Thereafter: 12,675 3 mg/kg at weeks 0, 2, and 6 then every 6 weeks[c] Year 1: 19,500 Thereafter: 17,550	 –$3,671 –$4,602 $229 $273

CZP = certolizumab pegol; EAP = Exceptional Access Program; NA = not applicable; Q2W = every two weeks; ODB = Ontario Drug Benefit; Q4W = every four weeks; vs. = versus.

[a] Yearly drug costs were based on patients within the weight range of 61 kg to 80 kg.

[b] Average of eight doses for the first year and 6.5 doses per year thereafter.

[c] Average of 10 doses for the first year and nine doses per year thereafter.

Source: ODB and ODB Formulary EAP (accessed December 2014) unless otherwise indicated.

TABLE 9: KEY LIMITATIONS

Identified Limitation	Description	Implication
Time Horizon		
Early discontinuation	The analysis does not look at the time at which discontinuation may occur	Given the higher cost for CZP in year 1 than some of the other biologic DMARDs, use of CZP may result in a greater cost to plans compared with certain other available biologic DMARDs
Long-term comparative effectiveness	[redacted]	A time horizon of longer than 1 year may not be appropriate
Treatment waning	Given the lack of long-term data for CZP in this indication, it is uncertain as to whether there would be any waning of treatment effect and whether this would differ from other treatments	May underestimate or overestimate the potential savings or costs
Based on MTC		
MTC: Harms	[redacted]	[redacted]
MTC: Study designs	[redacted]	[redacted]
MTC: Results at 12 weeks to 16 weeks	[redacted]	[redacted]
MTC: Study heterogeneity	[redacted]	[redacted]

Identified Limitation	Description	Implication
MTC: Conduct	[redacted]	[redacted]

ASAS = Assessment of SpondyloArthritis International Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CZP = certolizumab pegol; DMARDs = disease-modifying antirheumatic drugs; ITT = intention to treat; MTC = mixed treatment comparison; RCTs = randomized controlled trials.

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