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EXTENDED REPORT

Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study

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ABSTRACT

Background Women with chronic inflammatory diseases face uncertainty regarding the safety of biologics during breast feeding. CRADLE was the first industry-sponsored study to evaluate certolizumab pegol (CZP) concentrations in human breast milk and estimate average daily infant dose (ADID) of maternal CZP.

Methods CRADLE (NCT02154425) was a pharmacokinetic study of lactating mothers receiving CZP. After ≥3 CZP doses, breast milk samples were collected across one dosing period (14 days for 200 mg every 2 weeks [Q2W]; 28 days for 400 mg every 4 weeks [Q4W]). Optimal analytical methods were developed to determine CZP and polyethylene glycol (PEG) levels in breast milk. ADID and relative infant dose (RID) were estimated. Safety events in mothers and infants were assessed.

Results 19 CZP-treated mothers were screened; 17 entered the sampling period: 16 on 200 mg Q2W, 1 on 400 mg Q4W. 77/137 (56%) breast milk samples had no measurable CZP. For 4/17 mothers, all samples were below the lower limit of quantification (LLOQ). Estimated ADID was 0–0.0104 mg/kg/day; median RID: 0.15%. PEG was undetectable in 134/137 samples (results could not be determined in three samples). Infants of CZP-exposed mothers had a safety profile consistent with that of unexposed similar-age infants.

Conclusion When quantifiable, CZP concentrations were <3× LLOQ (<1% plasma concentration observed with therapeutic dose), indicating no/minimal CZP transfer from plasma to breast milk. RID was 0.15% of maternal dose; <10% is considered unlikely to be of clinical concern. No PEG transfer was observed. CZP absorption by infants via breast milk is unlikely due to its low oral bioavailability and Fc-free molecular structure. These findings are reassuring and support continuation of CZP treatment during breast feeding.

Trial registration number NCT02154425; Results.

INTRODUCTION

Women with chronic inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and Crohn's disease (CD) often experience postpartum flares.[1–4] Treatment of these conditions frequently involves monoclonal antibodies, such as anti-tumour necrosis factor (anti-TNF), and diffusion of these molecules into breast milk has been reported.[5 6] Existing evidence on anti-TNF transfer into breast milk lacks robust and systematic sample collection and assays validated in breast milk; reports are restricted to a few studies with a limited number of patients receiving infliximab,[7] adalimumab,[7 8] etanercept[9] or certolizumab pegol (CZP).[10 11] The lack of systematic collection of breast milk samples throughout dosing intervals, coupled with the absence of drug-specific assays validated in breast milk, suggests that existing data cannot be confidently translated into evidence-based clinical practice. Consequently, women treated with monoclonal antibodies who are considering breast feeding, as well as their physicians, face uncertainty regarding drug safety.[12]

Breast feeding is extremely important to child health and development.[13 14] Immunological and anti-inflammatory agents are passed on to the infant via breast milk, allowing development of protective mechanisms against several diseases.[15] In addition to creating an emotional bond between mother and child at an early stage, breast feeding has been associated with a decreased risk for sudden infant death syndrome[16] and other conditions.[17] Despite these benefits, the conflict between the risks of maternal medications needed for postpartum disease flare and ensuring optimal child nutrition through breast feeding presents a complex challenge.

Although biologics generally have very low oral bioavailability due to their large molecular size and the proteolytic environment in the digestive system,[18] the neonatal Fc receptor on human intestinal epithelial cells may promote uptake of undigested immunoglobulins (IgGs). CZP, the only PEGylated anti-TNF without an Fc region, has demonstrated efficacy for the treatment of RA,[19] CD,[20] axSpA[21] and PsA.[22] Physiologically, only minimal amounts of CZP are likely to cross into breast milk and be absorbed by the infant, due to its large molecule size and the replacement of the Fc portion with polyethylene glycol (PEG).[23]

The primary aim of CRADLE (NCT02154425), the first industry-sponsored, multicentre study to evaluate transfer of a biologic into breast milk, was to determine the concentrations of CZP in mature breast milk and to calculate the average daily infant dose (ADID), which is the daily CZP dose potentially ingested by the infant. Including multiple predefined sampling time points throughout the dosing interval allowed full characterisation of the

CZP pharmacokinetics (PK) in mature milk at steady state. The exploratory aim was to determine the breast milk concentrations of PEG. The relative infant dose (RID), which estimates the theoretical infant dose as a percentage of the weight-normalised maternal dose was calculated post hoc. Safety events in mothers and infants were examined.

METHODS

Study design and patients

CRADLE (NCT02154425) was a prospective, postmarketing, multicentre PK study to measure the CZP concentration in breast milk. It enrolled lactating mothers, at least 6 weeks postpartum with no upper age limit for infants, receiving commercial CZP for an approved indication (RA, CD, AS/axSpA and PsA), as prescribed by their treating physician. Importantly, the decision to treat with CZP and to breastfeed were made prior to and independently from study participation. CZP was not provided by the study sponsor.

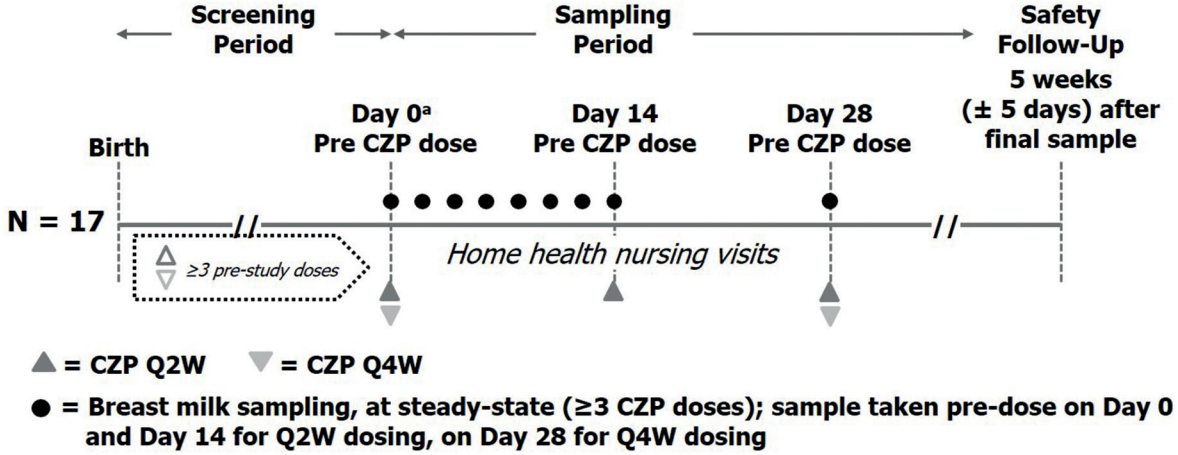
No exclusions were made regarding multiple births, but women who were pregnant, or planned to become pregnant during study duration, were ineligible to participate. Mothers with positive or indeterminate tuberculosis (TB) testing, active or latent TB infection or at high risk of TB infection were excluded, as were mothers who had received treatment with any biologic or anti-TNF other than CZP within five half-lives prior to collection of the first milk sample. Also excluded were mothers of premature infants (<37 weeks gestation). Mothers were withdrawn if they took any biological disease-modifying drug other than CZP during the sampling period. In addition, mothers with active mastitis were excluded from the sampling period until resolution.

The study was designed as a 'milk-only' study in accordance with the 2005 US Food and Drug Administration (FDA) draft guidance[24] and was conducted between September 2014 and October 2015 by six investigators: three in the USA, one in Switzerland and two in the Netherlands. In addition to traditional site-based enrolment, an open enrolment model was used in the USA and Canada, with remote oversight by a participating investigator. This enabled remotely located mothers to take part in the study without the burden of travel, thus allowing the study to reach more mothers meeting enrolment criteria than through traditional site-based enrolment alone. The study design and protocol were approved by the local ethics committee or institutional review board (IRB) at each participating site, or by a central IRB, as applicable. All mothers provided written informed consent to participate.

Study procedures

Mothers received commercial CZP on either the 2-weekly dose (CZP 200 mg every 2 weeks [Q2W]) or the 4-weekly dose regimen (CZP 400 mg every 4 weeks [Q4W]). After at least three CZP doses, when plasma CZP concentration in the mothers was considered at steady-state, mature breast milk samples were collected across a single dosing period. For mothers on CZP 200 mg Q2W, samples were collected on days 0, 2, 4, 6, 8, 10, 12 and 14; for mothers on CZP 400 mg Q4W, an additional sample was collected on day 28 (figure 1). All mothers were to dose on the same day as the first sample collection, with date and time of dosing being recorded by the home healthcare nurse. Predose samples were those collected on days 0 and 14 for mothers on CZP 200 mg Q2W, and on days 0 and 28 for mothers on CZP 400 mg Q4W. Compliance with CZP therapy was not mandated in the study; however, at day 0, all mothers were confirmed to have received at least three doses of CZP prior to the beginning of the sampling period.

In-home nursing visits for milk sample collection minimised the burden on mothers and were carried out at all study sites, using the same procedure: at each visit and at approximately the same time of day, milk was pumped from both breasts until completely emptied (accommodating the mothers' schedule), using the electronic breast pump (Medela Advanced Personal Double Pump) provided by the sponsor. Milk from both breasts was mixed by the home healthcare nurse, before 5 mL were placed on dry ice and shipped to the central laboratory (Quintiles; Atlanta [USA sites] or Edinburgh, UK [European sites]). During each visit, the nurse confirmed whether the infant had received any other nutrition in the prior 2 days to explore whether there was any difference between women who breast fed exclusively and those that supplemented breast feeding with other nutrition sources (eg, formula milk). To avoid interference by PEG-containing creams, mothers were only permitted to use PEG-free nipple/breast creams provided by the sponsor.



[a]Day 0 of the Sampling Period was ≥6 weeks post-delivery and when the patient was on an established CZP dose regimen (at least the third dose, regardless of CZP dosing schedule, but no maximum limit).

Figure 1 CRADLE study design. CZP, certolizumab pegol; Q2W, every 2 weeks; Q4W, every 4 weeks.

Samples were subsequently analysed at Covance Inc. (Chantilly, Virginia, USA). CZP concentration in breast milk was measured using an electro-chemiluminescence immunoassay, in which CZP was captured by a TNF-coated multiarray electrode and detected with an anti-PEG antibody, prior to reading on a Meso Scale Discovery (MSD; Rockville, Maryland, USA) platform.[25] The assay is CZP-specific and, due to the technical advantages of the MSD methodology (high sensitivity, large dynamic range, small sample volume[26 27]), >10 times more sensitive (lower limit of quantification [LLOQ]: 0.032 µg/mL) than the previous ELISA used in other CZP PK studies.[11 28 29] The assay was validated in milk; CZP stability in milk was confirmed.

The concentrations of total PEG (ie, PEG present as intact CZP or in deconjugated form) were determined by a validated assay using nuclear magnetic resonance spectroscopy (LLOQ: 0.5 µg/mL).[30]

Study endpoints

The primary objectives were to determine CZP concentrations in breast milk and to calculate the ADID of maternal CZP. The exploratory objective was to assess the concentration of total PEG in breast milk. A post hoc variable, RID, was calculated.[31] RID is the infant dose as a per cent of the weight-related maternal dose and is widely used by lactation specialists, paediatricians and neonatologists to assess risk to infants.[31 32] Analysis of the PK parameters was performed using Phoenix WinNonlin V.6.4 (Certara, USA).

The safety analysis included adverse events (AEs) in all mothers who received at least one dose of CZP and the infants of all participating mothers from the time of informed consent through safety follow-up (up to 5 weeks±5 days after the final sample was obtained). Patient consent was obtained after delivery, up to 10 weeks before day 0. Prior to sampling on day 0, eligibility was reconfirmed. During each sampling visit, patients were given the opportunity to report AEs spontaneously, and a general prompt using open-ended questions was also given. If an AE was reported during the in-home visit, the home healthcare nurse contacted the principal investigator to speak directly with the patient for further assessment.

AEs of interest included any opportunistic infections, malignancies (including unspecified), major adverse cardiac events, haematopoietic cytopaenias, serious bleeding, hepatic events and injection reactions (local or systemic).[32] AEs were coded using MedDRA V.18.1.

Statistical analysis

No formal sample size calculations were performed, as no statistical hypotheses were being tested. The planned sample size for the study was 16 mothers; approximately twice the minimum number of subjects considered sufficient by the FDA for a 'milk-only' study.[24] Summary statistics were reported for quantitative variables and frequency tables for qualitative data. Statistical analysis was performed using SAS V.9.3. All summaries of PK variables were based on the values observed at each visit: no imputation was used.

In addition to CZP concentrations, three measures of CZP transfer were considered: (1) the average daily CZP concentration in breast milk (C_{ave}), (2) ADID and (3) RID. C_{ave} is calculated by non-compartmental analysis from the concentration versus time profile over the dosing interval, using the actual sampling days. ADID is the dose of CZP ingested by a child based on C_{ave} and the estimated daily volume of milk ingested. As per the 2005 FDA draft guidance,[24] the standardised milk consumption of a fully breastfed 2-month-old infant (150 mL/kg/day) was used to calculate the ADID over a dosing interval (14 or 28 days) from the study data:

$$Estimated\ ADID\ \left(mg/kg/day\right) = C_{average} \times 150\,mL/kg/day$$

The exploratory post hoc variable, RID, was calculated as follows[31]:

$$RID\ (\%) = \frac{ADID\ \left(mg/kg/day\right)}{Maternal\ dose\ \left(mg/kg/day\right)} \times 100$$

RID was not calculated when all results were below the lower limit of quantification (BLQ), as was the case in four mothers.

Subgroup analyses were performed, based on the mothers' indications (RA, CD and PsA) and on the use of supplemental nutrition (non-exclusive vs exclusive breast feeding) for the PK parameters. Subgroup analyses were not performed on groups with fewer than three patients (axSpA).

RESULTS

Patients

Between 8 September 2014 and 30 October 2015, 19 mothers were screened; 18 received commercial CZP and met the inclusion criteria (one mother was prescribed CZP prior to screening, but did not receive CZP and was therefore ineligible). One mother failed screening and discontinued the study due to an AE of herpes zoster. All 17 mothers who entered the sampling period completed the study (no missed visits);

Table 1 Demographics and baseline characteristics of mothers and infants

	All mothers (n=18)*
Mean (SD), unless otherwise stated	
Age, years	33.7 (4.2)
Weight, kg	68.9 (9.6)†
BMI, kg/m²	23.6 (3.0)†
Location, n	
USA/Canada‡	10
Switzerland	5
The Netherlands	3
Mother's indication for CZP treatment, n†	
Rheumatoid arthritis	7
Crohn's disease	5
Psoriatic arthritis	3
Axial spondyloarthritis/ankylosing spondylitis	2
	All infants (n=17)
Median (min–max), unless otherwise stated	
Female, n (%)	11 (64.7)
Gestational age at birth, weeks	40.0 (39.0–41.7)
Weight at birth, kg	3.5 (2.6–4.1)
Length at birth, cm	50.7 (48.0–57.0)
Age at time of mother's first sample, months	2.8 (1.6–16.8)
Age at time of mother's first sample, n (%)	
≤6 months	13 (76.5)
>6 months–≤12 months	2 (11.8)
≥12 months–≤18 months	2 (11.8)

*Includes one screen failure.
†n=17.
‡One Canadian patient enrolled under the central USA site, which was approved by the Canadian central IRB.
BMI, body mass index; IRB, institutional review board.

Table 2 Concentrations of CZP (µg/mL) in breast milk after administration of CZP dose in mothers

Mother number	Relative time (days)								
	0	2	4	6	8	10	12	14	28
17	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
4	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	–
13	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	–
14	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	–
7	BLQ	BLQ	BLQ	BLQ	BLQ	0.035	BLQ	BLQ	–
6	BLQ	BLQ	0.044	0.048	BLQ	BLQ	BLQ	BLQ	–
8	BLQ	BLQ	0.035	0.034	0.043	BLQ	BLQ	BLQ	–
10	BLQ	BLQ	BLQ	0.033	0.042	0.042	BLQ	BLQ	–
12	BLQ	BLQ	0.034	0.037	0.033	BLQ	BLQ	BLQ	–
2	BLQ	BLQ	0.035	0.037	0.041	BLQ	0.043	BLQ	–
11	BLQ	BLQ	0.051	0.038	0.042	BLQ	0.033	BLQ	–
15	BLQ	BLQ	0.041	0.034	0.033	BLQ	0.037	BLQ	–
16	0.040	0.033	0.036	0.037	0.043	BLQ	BLQ	BLQ	–
3	BLQ	0.032	0.049	0.053	0.037	0.037	0.033	0.033	–
9	0.039	0.040	0.047	0.045	0.042	0.043	0.038	0.035	–
1	0.057	0.051	0.066	0.065	0.062	0.056	0.052	0.041	–
5	0.056	0.069	0.074	0.076	0.076	0.069	0.069	0.060	–

White coloured areas depict CZP concentration Less than 3×LLOQ (<0.096 µg/mL).
Grey coloured areas depict CZP concentration Less than 2×LLOQ (<0.064 µg/mL).
Dark grey coloured areas depict CZP concentration BLQ (<0.032 µg/mL).
Days 0 and 14 are predose for mothers on the CZP 200 mg Q2W dosing regimen.
Days 0 and 28 are predose for the mother on the CZP 400 mg Q4W dosing regimen.
For reference, the mean 12-week CZP plasma C_{trough} value, that is, the trough concentration at steady-state, reported from non-pregnant patients with RA receiving CZP 200 mg Q2W in the RAPID2 trial was 15.7 µg/mL (95% CI 14.0 to 17.7).[28]
BLQ, below the lower limit of quantification, <0.032 µg/mL; CZP, certolizumab pegol; LLOQ, lower limit of quantification; Q2W, every 2 weeks; Q4W, every 4 weeks; RA, rheumatoid arthritis.

100% of planned samples were collected. Seven mothers (38.9%) were diagnosed with RA, 5 (27.8%) with CD (two of which also had rheumatic diseases), 3 (16.7%) with PsA and 2 (11.1%) with axSpA. The demographics and baseline characteristics of all mothers screened and of all infants of participating mothers are shown in table 1. The mothers' indications for CZP treatment and their infants' age at the time of first sampling are listed in online supplementary table 1.

Pharmacokinetic results

One hundred thirty-seven breast milk samples were collected from 17 mothers (16 on CZP 200 mg Q2W, one on CZP 400 mg Q4W). All samples had CZP concentrations that were minimal or BLQ. Importantly, 77/137 (56%) samples had no measurable CZP (table 2). Four of the 17 women, including one on CZP 400 mg Q4W, did not have measurable CZP levels in their breast milk at any time point. In the remaining 13 mothers with a measurable concentration during at least one time point, the highest CZP concentration was 0.076 µg/mL, less than three times LLOQ (0.032 µg/mL).

The estimated ADID ranged from 0 to 0.0104 mg/kg/day; median estimated ADID was 0.003503 mg/kg/day (table 3). Additional CZP PK parameters are shown in table 3. The RID, calculated post hoc,[31 32] ranged from 0.04% to 0.30%; median RID was 0.15%.

PK parameters were similar for women with different indications as well as between mothers using supplemental nutrition and those breast feeding exclusively.

Table 3 Pharmacokinetic parameters of CZP in breast milk after administration of CZP

Parameter	n	Geo. mean (Geo. CV (%))	Median (min–max)
All mothers: both CZP 200 mg Q2W and CZP 400 mg Q4W dosing regimens			
Estimated average daily infant dose (mg/kg/day)	17	0.00426 (59.4)	0.003503 (0–0.0104)
C_{ave} (µg/mL)	17	0.0248 (58.0)	0.02335 (0.00744–0.0693)
t_{max} (day)	13	–	5.051 (2.89–11.9)
Mothers on CZP 200 mg Q2W dosing regimen only			
AUC_T (day* µg/mL)	13	0.398 (59.4)	0.4249 (0.104–0.970)
C_{max} (µg/mL)	16	0.0383 (50.3)	0.04285 (BLQ–0.0758)

AUC_T, area under the curve over a dosing interval (14 or 28 days); C_{ave}, average concentration over a dosing interval; C_{max}, maximum observed CZP concentration in milk over the dosing interval; CV, coefficient of variations; CZP, certolizumab pegol; Geo.: geometric; Q2W, every 2 weeks; Q4W, every 4 weeks; t_{max}, time of the maximum observed concentration.

Table 4 Adverse events (AEs) occurring in mother-infant pairs

Mothers			Infants		
Mother (n=18)*	No. of AEs in mother (n)	AE	Infant (n=17)*	No. of AEs in infant (n)	AE
1	None		1	2	Lichen striatus Upper respiratory tract infection
2	1	**Breast abscess‡**	2	None	
3	None		3	1	Gastro-oesophageal reflux disease
5	1	Rash	5	1	Nasopharyngitis
7	1	Upper respiratory tract infection	7	1	Upper respiratory tract infection
8	2	Candida infection Crohn's disease flare	8	1	Candida infection
10	1	Viral upper respiratory tract infection	10	None	
11	1	Headache	11	None	
13	1	Psoriatic arthritis flare	13	None	
14	2	Nipple disorder Headache	14	2	Vomiting Nasopharyngitis
15	*None*		15	1	Nasopharyngitis
16	2	Upper respiratory tract infection Pneumonia	16	2	Upper respiratory tract infection Nasopharyngitis
SF†	2	Herpes zoster Galactostasis	N/A		
Total number of mothers experiencing any AE		10	Total number of infants experiencing any AE		8
Total number of AEs		14	Total number of AEs		11

The safety analysis included all mothers who received at least one dose of CZP and the infants of all mothers who participated in the study. The safety follow-up period extended up to 5 weeks (±5 days) after the final sample was collected. AEs in mother-infant pairs were not necessarily associated temporally.
Bold text indicates serious adverse event (SAE).
*Mother-infant pairs are numbered as per table 2.
†SF, screen failure: mother discontinued from study due to AE of herpes zoster during screening period.
‡Breast abscess during screening period, which resolved prior to sampling.
CZP, certolizumab pegol; N/A, not applicable as the mother did not enter the sampling period.

PEG concentration was analysed in 137 samples; 134 samples had no quantifiable PEG; three samples were classed as not reportable (online supplementary table 2).

Safety

The safety analysis included 18 CZP-exposed mothers and 17 infants. AEs are shown in table 4. One mother discontinued the study during the screening period due to an AE of herpes zoster. Overall, 10 mothers (55.6%) experienced 14 AEs, and 8 infants (47.1%) experienced 11 AEs.

AEs in mothers and infants were mostly mild to moderate in intensity (mothers: three mild [16.7%] and six moderate [33.3%]; infants: six mild [35.3%] and two moderate [11.8%]). One severe AE (5.6%) was reported in one mother: a breast abscess, which occurred during the screening period and was resolved prior to sampling. Five AEs in four mothers were classified as drug-related: two (11.1%) upper respiratory tract infections, and one each (5.6%) of herpes zoster, CD flare and pneumonia. Nasopharyngitis in one infant (5.9%) was considered mild in intensity and classified as drug-related by the principal investigator, based on the known CZP safety profile.[33] No serious AEs were reported in the infants. Overall, events in the mothers were consistent with the known CZP safety profile, and the events observed in infants were consistent with those in unexposed infants of similar age.[34–36]

DISCUSSION

CRADLE was the first industry-sponsored clinical lactation study evaluating the transfer of a biologic into mature breast milk of women with chronic inflammatory diseases. Because low levels of IgGs have been shown to diffuse into breast milk,[5] it is important to measure the relative abundance of therapeutic antibodies in breast milk.[32] This study found minimal transfer of CZP into breast milk, with an infant receiving, on average, 0.15% (RID) of the maternal dose.

While prior studies entailed case reports with few milk samples obtained at varying times after dosing,[37 38] CRADLE was designed to fully characterise the CZP PK profile in mature milk at steady-state. Following the FDA recommendation and in line with the 2005 guidance for industry,[24] the study was designed as a 'milk-only' study. The rationale was that the CZP PK profile was already well established[28] and that lactation was not expected to substantially change its PK. In addition, this 'milk-only' study design avoided additional burden on mothers and their babies: milk sampling did not occur earlier than 4–6 weeks postpartum to ensure that lactation and feeding patterns were well established, mature milk was being produced and maternal physiology had largely returned to pre-pregnancy state.

CZP concentration was BLQ in 56% of milk samples. When measurable, CZP concentrations were less than 3× LLOQ, with a marginal maximum concentration (0.0758 µg/mL). This is equivalent to less than 1% of the expected mean CZP plasma

trough concentration for a CZP-treated adult,[28 39] indicating no to minimal transfer of CZP from plasma to breast milk. No transfer of total PEG from plasma to breast milk was observed.

The estimated daily dose of CZP ingested by breastfed infants over the dosing interval was minimal, with maximum ADID of 0.0104 mg/kg/day. The median CZP RID was 0.15%. The number of medications available to breast feeding mothers requiring drug therapy is increasing, and RID is a useful parameter for assessing drug safety in breastfeeding by providing a standardised means of referencing infant to maternal exposure on a dose/weight basis.[31] An RID <10% is considered safe by lactation specialists, with the estimate evaluated against the potential toxicity of the drug.[31 32 40] Examples of drugs considered safe when breast feeding include analgesics (ibuprofen and acetaminophen), antibiotics (penicillins and cephalosporins), antidepressants (citalopram and sertraline) and anticoagulants (heparin and dalteparin) (RID <10%).[40]

Subgroup analyses suggest that transfer of CZP into breast milk is independent of the mother's indication and CZP dosing regimen. Additionally, no difference between subgroups was observed regarding CZP transfer into milk of exclusively breastfeeding mothers versus those who supplemented nutrition.

Although there were no enrolment restrictions for patient numbers for the two dosing regimens, 16/17 patients were on the single dose regimen, as per physician discretion. To our knowledge, this does not impact the results' relevance.

Enrolment for studies of this nature is challenging, given the unique barriers to participation, such as ethical, legal and medical considerations associated with this sensitive patient population. The CRADLE open enrolment, combined with the traditional site-based model, and including in-home nursing services, allowed mothers to participate without the burden of travel. This operational model was essential to the successful completion of the study.

We acknowledge that no preterm babies were included in this study, although it is well known that prematurity is an underlying risk for women with inflammatory diseases, particularly those with high disease activity.[41] It is noteworthy that while valuable data might be obtained from studying drug absorption in premature babies, due to the possible differences in their digestive tracts from full-term infants,[42] such an analysis would have been outside the scope of this study.

Similarly, milk collection from mothers immediately after birth was not included for a number of reasons: due to the very limited volume of breast milk/colostrum available at this time, obtaining these samples would be challenging and, in addition, the study did not wish to disrupt the initial mother/infant bonding. These limitations raise awareness for the need of further research into drug transfer from mother to infant.

No new CZP safety issues were identified. AEs in mothers were consistent with the current CZP safety profile, while events in infants were consistent with those occurring in unexposed infants of similar age. For reference, incidence for minor infections in infants is 6–8 times per year for upper respiratory tract infection/nasopharyingitis[34 35] and 2%–5% for oral candidiasis.[36]

In conclusion, these findings suggest that the level of CZP ingested by the suckling infant is minimal and indicate that continuation of CZP treatment is compatible with breast feeding. The robust clinical evidence from the CRADLE study allows breastfeeding women with chronic inflammatory diseases and their treating physicians to make informed decisions regarding their postpartum treatment.

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