Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies

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Background: Sepsis and bacterial meningitis are major causes of mortality and morbidity in neonates and infants. Meropenem, a broad-spectrum antibiotic, is not licensed for use in neonates and infants below 3 months of age and sufficient information on its plasma and CSF disposition and dosing in neonates and infants is lacking.

Objectives: To determine plasma and CSF pharmacokinetics of meropenem in neonates and young infants and the link between pharmacokinetics and clinical outcomes in babies with late-onset sepsis (LOS).

Methods: Data were collected in two recently conducted studies, i.e. NeoMero-1 (neonatal LOS) and NeoMero-2 (neonatal meningitis). Optimally timed plasma samples (n = 401) from 167 patients and opportunistic CSF samples (n = 78) from 56 patients were analysed.

Results: A one-compartment model with allometric scaling and fixed maturation gave adequate fit to both plasma and CSF data; the CL and volume (standardized to 70 kg) were 16.7 (95% CI 14.7, 18.9) L/h and 38.6 (95% CI 34.9, 43.4) L, respectively. CSF penetration was low (8%), but rose with increasing CSF protein, with 40% penetration predicted at a protein concentration of 6 g/L. Increased infusion time improved plasma target attainment, but lowered CSF concentrations. For 24 patients with culture-proven Gram-negative LOS, pharmacodynamic target attainment was similar regardless of the test-of-cure visit outcome.

Conclusions: Simulations showed that longer infusions increase plasma PTA but decrease CSF PTA. CSF penetration is worsened with long infusions so increasing dose frequency to achieve therapeutic targets should be considered.

Introduction

Sepsis and bacterial meningitis are major causes of mortality and morbidity in neonates and infants and can be considered as part of a single continuum in that septic infants can develop meningitis.1,2 Late-onset sepsis (LOS) is defined as sepsis starting 72 h or more after birth.

Meropenem is a broad-spectrum carbapenem antibiotic with activity against common pathogens causing neonatal sepsis and meningitis. It is bactericidal against Escherichia coli, Klebsiella spp., Enterobacter spp. and Pseudomonas spp., which are known to cause LOS, and also against pathogens responsible for bacterial meningitis such as Streptococcus agalactiae (i.e. group B streptococci), E. coli, Listeria monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis.3,4

Meropenem pharmacodynamics (PD) is usually described by the percentage of time when concentrations are above the MIC (%T>MIC). Approximately 40%T>MIC is believed to be sufficient for a bactericidal effect;5,6 however, for immunocompromised patients, including neonates, higher targets have been suggested7 and a recent study looking at meropenem PD indices determined the PD target for neonates to be 61%T>MIC.8 For lower respiratory tract...
infections, %T > 5 × MIC was suggested.\textsuperscript{9} Meropenem is predominantly renally eliminated and approximately 75% is excreted unchanged in the urine.\textsuperscript{10,11} As a polar, hydrophilic molecule, meropenem’s penetration into the CSF through the blood–brain barrier is limited under normal, healthy conditions, but this may increase when the meninges are inflamed.\textsuperscript{12,13}

Meropenem is currently unlicensed in infants below 3 months of age and, whilst there are studies describing its pharmacokinetics (PK) in neonates and infants,\textsuperscript{14–18} only Smith et al.\textsuperscript{15} studied both plasma and CSF concentrations, including single CSF concentrations from only six patients. Since the concentration–time profile of meropenem differs between plasma and CSF, taking the ratio of CSF to plasma is confounded by time after dose. To correctly assess the fractional CSF penetration necessitates sufficient sample numbers and timing for a model-based estimation. Consequently, sufficient information on meropenem’s disposition to infer dosing in this population is lacking. The NeoMero Consortium recently completed two studies with PK sampling from both plasma and CSF: NeoMero-1 [‘Efficacy, pharmacokinetics and safety of meropenem in subjects below 90 days of age (inclusive) with clinical or confirmed late-onset sepsis: a European multicentre randomised phase III trial’] compared meropenem with standard of care (β-lactam plus aminoglycoside);\textsuperscript{19} and NeoMero-2 [‘Pharmacokinetics and safety of meropenem in subjects below 90 days of age (inclusive) with probable and confirmed meningitis: a European multicentre phase I–II trial’]. Since some patients recruited to NeoMero-1 developed meningitis and transferred to NeoMero-2, the aim of this study was to report a joint analysis of the plasma and CSF PK results from both studies. We further sought links with outcome (PD) in NeoMero-1 (LOS) in order to inform dosing for LOS.

Patients and methods

Ethics

In NeoMero-1, subjects were recruited from 15 centres in six different countries (Estonia, Greece, Italy, Lithuania, Spain and Turkey). There were, on average, 8 subjects/centre (range 1–25). In NeoMero-2, there were 21 centres in seven countries (Estonia, Greece, Italy, Lithuania, the Netherlands, Spain and the UK) recruiting, on average, 2 subjects/centre (range 1–9). Independent Ethics Committees in each country approved the studies, which were registered on EudraCT (2011-001515-31 and 2011-001521-25) and clinicaltrials.gov (NCT01551394 and NCT01556124).

Patient recruitment

The inclusion criteria for NeoMero-1 were: diagnosis of sepsis and postnatal age (PNA) ≤ 90 days, and > 72 h of life at sepsis onset. Sepsis was defined as: (i) sepsis confirmed by a positive bacterial culture, accompanied by an abnormal clinical or laboratory measurement; or (ii) clinical sepsis, i.e. in as: (i) sepsis confirmed by a positive bacterial culture, accompanied by an abnormal clinical or laboratory measurement; or (ii) clinical sepsis, i.e. in

PK modelling

PK modelling was undertaken using the first-order conditional estimation method with interaction (FOCEI) in NONMEM 7.3 (ICON Development Solutions, Ellicott City, MD, USA).\textsuperscript{24} Firstly the plasma model was determined, followed by addition of a compartment for the CSF concentrations. For the plasma PK, one-, two- and three-compartment structural models were tested to define the basic structural model. Between-subject variability was assumed to follow a log-normal distribution, and for the residual error, proportional, additive, combined and Box–Cox power transformation (with
both the shape and the scedasticity parameters estimated\(^{25}\) were tested. To delineate size and age from other possible covariates, body weight and postmenstrual age were included a priori in the model with allometric weight scaling and a function describing renal function maturation, respectively.\(^{26}\) The parameters of the maturation function were fixed to values from a previous study of human glomerular filtration development.\(^{27}\) However, since meropenem is renally cleared, and renal function improves in the days after birth independently of postmenstrual age, we also tested the effects of PNA and serum creatinine (corrected for postmenstrual age\(^{28}\)) on CL. A covariate was included in the final model, if (after the inclusion) it produced a drop in the objective function value (OFV) (\(\Delta\text{OFV}\)) of \(>6.63\), which corresponds to a P value of \(<0.01\). The significance of a covariate was also tested by a randomization test\(^{28,29}(n = 1000)\) performed using PsN.\(^{31}\) Since most patients were expected to contribute one CSF sample, the CSF volume was fixed to 0.15 L/70 kg\(^{12}\) and so two parameters were estimated: the inter-compartmental CL between plasma and CSF, and the fraction of meropenem penetration from the central compartment into the CSF. Markers of CNS inflammation (CSF proteins, lactate concentration, glucose concentration or number of white blood cells per unit of volume) may correlate with blood–brain barrier function; therefore, the effects of these covariates on penetration fraction were investigated. When these covariates were missing, they were replaced with the median.

Basic goodness-of-fit plots (observations versus predictions, conditional weighted residuals (CWRES) versus time and prediction) in addition to visual predictive checks with 1000 replicates were used during model-building and to select the final model. A non-parametric bootstrap analysis was performed (\(n = 1000\)) on the final model to test parameter robustness and derive uncertainty around the parameter estimates.

**PD analysis of LOS**

For NeoMero-1 patients with culture-proven Gram-negative bloodstream infections for which an MIC could be determined and who received at least 24 h of treatment, the model was used to generate individual AUC\(_0\text{}\text{MIC}, C_{\text{max:MIC}}, C_{\text{min:MIC}}\) and %\(T\geq\text{MIC}\). These were compared with whether the patient successfully completed the treatment course with clinical/labouratory improvement (success) or if treatment had to be modified at the discretion of the treating physician or the patient died (failure). These endpoints were measured at the test-of-cure visit 2 days after the end of planned therapy (11 ± 3 days). The Kruskal–Wallis test was used to compare the two groups.

**Simulations**

Monte Carlo simulations (\(n = 1000\)) using the final model estimates were used to generate \(\%T\geq\text{MIC}\) curves for different dosing regimens and the following MIC values: 0.25, 0.5, 1, 2, 4, 8 and 16 mg/L. The unbound fraction of meropenem was fixed to 0.98.\(^{31}\) The \(\%T\geq\text{MIC}\) curves were generated using plasma (for LOS) or CSF (for meningitis) predictions. The PD target was set to 61%\(T\geq\text{MIC}\)\(^3\) and simulations were done for all four age groups.

**Results**

**Demographics and PK samples**

A total of 167 patients underwent PK sampling in the NeoMero studies, with 123 from NeoMero-1 (5 of whom were diagnosed with probable or confirmed bacterial meningitis and transferred to NeoMero-2) and 49 (including the 5 from NeoMero-1) in NeoMero-2. At enrolment, their median (range) weight was 2.12 (0.48–6.32) kg, PNA was 13 (1–90) days and gestational age (GA) was 33.3 (22.6–41.9) weeks. Patients from the NeoMero-1 study were more premature (median GA of 31.9 weeks versus 37.1 weeks in NeoMero-2) and therefore also weighed less than the patients from the NeoMero-2 study. Demographics are presented in Table 1.

Three optimally timed plasma samples were collected from 109 patients, whilst 44 provided a single trough sample. Sampling numbers from the remaining patients were two (nine patients), four (four patients) and seven (one patient). There was an even spread in PNA and GA of optimally timed samples with 25, 18, 20 and 24 patients, respectively, providing three optimal samples in each of the pre-defined age categories (<2 weeks GA and <2 weeks PNA; <2 weeks GA and >2 weeks PNA; >2 weeks GA and <2 weeks PNA; and >2 weeks GA and >2 weeks PNA). Following sample analysis, 11 meropenem peak plasma samples were below 10 mg/L indicating possible data entry error and were thus excluded from the analysis to prevent biasing the model development. The influence of these data points was tested with the final plasma model and, although the changes in the typical final model parameter estimates were below 10%, the interindividual variability and the uncertainty approximately doubled, again giving a reason for their exclusion. The data set for model-building therefore contained 401 plasma samples and 78 CSF samples (CSF was obtained from 56 patients). The median (range) of CSF sampling time was 5.27 (0–12.0) h post-dose. Plots of the raw data are presented in Figure 1. One CSF protein concentration was also excluded from the analysis, as it was not deemed biologically plausible (102 g/L).

**Meropenem clearance is significantly related to renal function, and CSF penetration to CSF protein concentration**

The final plasma population PK model was a one-compartment model. Weight was included with allometric scaling (with exponents fixed to 1 for central volume and 0.632 for CL\(^{22}\)) and postmenstrual age was included with a maturation function (with parameters fixed to values from a study of renal development\(^{27}\)). PNA did not significantly improve the model fit; however, serum creatinine concentration (standardized by postmenstrual age) proved to have a significant effect on meropenem clearance (\(\Delta\text{OFV of 19.7}\)) and was therefore also included in the final model.

An additional compartment was added to describe meropenem CSF PK and to estimate the penetration of meropenem from plasma to the CSF. Out of the tested covariates, both the CSF lactate concentration and the CSF total protein concentration proved to significantly explain the CSF penetration (\(\Delta\text{OFVs of 24.3 and 24.4, respectively}\)). However, since there were fewer missing measurements for CSF protein concentration (there were 86 protein and 54 lactate concentrations available, with 58 and 41 of these, respectively, taken at the time of CSF meropenem sampling), this covariate was included in the final model. The significance of the covariates was also confirmed by a randomization test\(^{29,30}\).

Initially, a proportional model was chosen for the residual error of both plasma and CSF data; however, Box–Cox power transformations of the residual error\(^{30}\) resulted in an improved fit (\(\Delta\text{OFV of 67.8}\)) and there was an improvement in the distribution of the residuals; therefore, this residual error model was used. The estimate for the scedasticity parameter corresponding to the CSF concentrations was approximately zero and there was no
There was no difference in AUC0–24:MIC ratio (per our study dosing).

The diagnostic plots showed adequate fit to the data (i.e. agreement between the measured and predicted concentrations was observed and there was no particular trend in the residual plots) (Figure 2) and the visual predictive check (using 1000 replicates) confirmed that the model had good simulation properties (Figure 3).

In vitro PD target reached in all culture-proven cases

In the NeoMero-1 study there were 24 individuals with culture-proven LOS with a Gram-negative organism for which MIC values were available and at least 24 h of meropenem had been administered. Of these, 12 patients were considered to have been successfully treated (no need to modify the treatment course), whereas 12 patients failed (2 died, 9 required treatment modification at the discretion of the treating physician and 1 still had unresolved symptoms). The mean MIC in the 12 successes was 0.27 mg/L, whereas in the 12 failures the mean MIC was 0.98 mg/L (Figure 3).

The simulations in Figure 5 show that the same dose given as a continuous infusion achieves higher \( C_{\text{min}} \) concentrations in CSF than in plasma, and so a comparison of 20 and 40 mg/kg bolus versus continuous infusion are shown in Figure 5 (with a frequency of 8 hourly or 12 hourly for those <32 weeks gestation and <2 weeks PNA as per our study dosing).

### Table 1. Demographics of included subjects

|                       | All data         | NeoMero-1       | NeoMero-2       |
|-----------------------|------------------|----------------|----------------|
| Number of subjectsa   | 167              | 123            | 49             |
| Weight (kg), median (range) | 2.12 (0.48–6.32) | 1.68 (0.48–5.01) | 3.11 (0.60–6.32) |
| GA (weeks), median (range) | 33.3 (22.6–41.9) | 31.9 (22.6–41.3) | 37.1 (23.4–41.9) |
| PNA (days), median (range) | 13 (1–90)       | 15 (3–83)      | 9 (1–90)       |
| Postmenstrual age (weeks), median (range) | 37.4 (23.7–51.3) | 36.0 (23.7–51.3) | 38.8 (24.9–51.1) |
| Female, n (%)         | 78 (46.7)        | 59 (48.4)      | 19 (42.2)      |
| Number of plasma samples | 401             | 255            | 147            |
| Plasma samples per patient, mean | 2.4             | 2.1            | 3.0            |
| Number of CSF samples  | 78               | 32             | 46             |
| CSF samples per patient, mean | 0.47           | 0.26           | 0.94           |
| Plasma concentration (mg/L), median (range) | 7.94 (0.01–147.7) | 5.27 (0.01–147.7) | 12.4 (0.1–139.0) |
| CSF concentration (mg/L), median (range) | 1.58 (0.04–35.4) | 1.23 (0.04–7.34) | 1.90 (0.05–35.4) |
| Plasma time after the dose (h), median (range) | 5.66 (0–12.4)  | 5.93 (0–12.4)  | 5.19 (0–12.2)  |
| CSF time after the dose (h), median (range) | 5.27 (0–12.0)  | 5.99 (0–12.0)  | 5.03 (0–11.5)  |
| Creatinine (\( \mu \text{mol/L} \)), median (range) | 32.0 (3.54–197.4) | 34.5 (3.54–197.4) | 27.0 (6.0–133)  |
| C-reactive protein (mg/L), median (range) | 23.0 (0.3–280) | 23.2 (0.3–242) | 22.4 (0.4–280) |
| Procalcitonin (ng/mL), median (range) | 2.7 (0.1–377.2) | 2.8 (0.1–128.6) | 1.8 (0.1–377.2) |

For creatinine, C-reactive protein and procalcitonin, the summary statistics represent all samples recorded during the study. Day 0 = first day of life.

Weight, PNA and GA–at enrolment.

aFive infants switched from NeoMero-1 to NeoMero-2.

### Discussion

This population PK model describing plasma and CSF disposition of meropenem in infants aged <90 days with LOS and/or bacterial meningitis represents the largest study of meropenem PK in infants aged <90 days to have been reported to date, which also included the highest number of collected CSF samples in this population. The generally accepted target of 40%\( T_{\text{MIC}} \) is believed to be adequate for bactericidal effects of carbapenems, but a recent in vitro study has suggested that differences in the PK profile in neonatal patients means a higher target of 61%\( T_{\text{MIC}} \) is warranted. All of our patients with culture-proven Gram-negative LOS achieved this target, but it should be noted that most MIC values were ≤0.25 mg/L. Simulations showed that 90% of patients should achieve 61%\( T_{\text{MIC}} \) for organisms with an MIC of ≤2 mg/L and so our major finding is that, for meropenem-susceptible organisms, a 20 mg/kg bolus appears to be a sufficient dose for LOS (Figure 5).

A recent randomized controlled trial of continuous versus 30 min meropenem infusion in neonates with culture-proven infection found decreased mortality and ventilator support required in the continuous infusion group. Whilst no MICs were recorded in this study, which also found surprisingly high failure of microbial eradication at 7 days (30% overall), it is not the only clinical study to report improved outcomes with differing meropenem \( C_{\text{min}} \). High %\( T_{\text{MIC}} \) has also been reported to be associated with improved clinical outcomes in adult lower respiratory tract infection, with a breakpoint of \( C_{\text{min}} \) of 5 times the MIC being associated with maximum benefit.

The simulations in Figure 5 show that the same dose given as a continuous infusion achieves higher \( C_{\text{min}} \)-MIC ratios. Simulations...
from our model based on a breakpoint of 2 mg/L showed that standard 20 mg/kg dosing would achieve the in vitro-derived target of 61% $T_{\text{MIC}}$ in 90% of patients, but if the MIC were to increase to 4 mg/L as organisms become intermediately resistant, it would be necessary to increase dosing to 40 mg/kg. The use of a continuous infusion with an 8-hourly dose of 40 mg/kg (i.e. 120 mg/kg in 24 h) would be required to achieve a $C_{\text{min}}$;MIC ratio of $>5$ for an MIC of around 1 mg/L and continuous infusions do clearly increase plasma $\%T_{\text{MIC}}$ (Figure 5). Simply moving to continuous infusions may, however, not be appropriate, particularly in this clinical setting where patients with LOS can go on to develop meningitis. As can be seen in Figure 5, continuous infusions give substantially lower CNS concentrations for the same total daily dose. This is likely due to low $C_{\text{max}}$ resulting in lower peripheral concentrations. The association between longer meropenem infusions and lower $C_{\text{max}}$ has also been previously shown.

The data in our study have substantially increased the literature on meropenem CSF PK, which enables simulated dosing schemes to balance circulating and CSF concentrations. The only study that focused on meropenem plasma and CSF disposition in infants (<3 months of age) to date involved six patients, who provided nine CSF samples. Smith et al. reported that uptake of meropenem into the CSF was 70%, determined by comparing plasma and CSF concentrations at the same timepoint. This method is suboptimal since the CSF and plasma time courses vary as $\beta$-lactams enter the CSF through paracellular pathways, resulting in a delayed peak CSF concentration. Our model-based typical estimate for the fraction of meropenem penetration from plasma into the CSF was 8.4%, which is at the lower end of the values previously reported in the literature: 10% up to 30%, or 40% and this could be because the meninges were not inflamed in many of the NeoMero-1 patients without meningitis; median CSF protein concentration exceeded 6 g/L. We did find a significant increase in CNS penetration with increasing CSF protein concentration exceeded 6 g/L. Overall the CNS penetration results show that the fraction entering the CNS is low and comparable with other populations, although when inflammation is present, as evidenced by the presence of proteins in the CSF, penetration significantly increases.

The values of the PK parameters for a typical infant from this study (weight = 2.1 kg, postmenstrual age = 37.4 weeks, serum creatinine = 32 $\mu$mol/L, CSF protein concentration = 1.2 mmol/L and serum creatinine, standardized by postmenstrual age = 60 $\mu$mol/L) were: CL = 0.39 L/h and $V = 1.17$ L. These values

![Figure 1. Plot of meropenem concentration versus time after dose for plasma and CSF. The top two plots show data for NeoMero-1 and the bottom two plots show data for NeoMero-2. Data points from the same individual are joined with a broken line (these are not always taken from the same dosing interval).](https://academic.oup.com/jac/article-abstract/73/7/1908/4978317)
Table 2. Population PK model final parameter estimates

|                          | Mean    | SE     | %CV   | η-shrinkage (%) | Bootstrap, median (95% CI) |
|--------------------------|---------|--------|-------|----------------|---------------------------|
| CL (L/h/70 kg)           | 16.7    | 1.07   | —     | —              | 16.7 (14.7, 18.9)         |
| θ_creatinine             | −0.40   | 0.094  | —     | —              | −0.40 (−0.58, −0.21)      |
| V (L/70 kg)              | 38.6    | 2.15   | —     | —              | 38.6 (34.9, 43.4)         |
| CL_CSF (L/h/70 kg)       | 0.017   | 0.004  | —     | —              | 0.016 (0.001, 0.030)      |
| CSF uptakea              | 2.39    | 0.205  | —     | —              | 2.38 (2.01, 2.82)         |
| θ_CSF proteinsa          | −0.17   | 0.110  | —     | —              | −0.17 (−0.43, 0.015)      |
| IIV on CL                | 0.255   | 0.058  | 50.5  | 13.5           | 0.248 (0.154, 0.370)      |
| IIV on V                 | 0.153   | 0.059  | 39.1  | 31.0           | 0.154 (0.042, 0.282)      |
| Cov IIV CL-V             | 0.167   | 0.055  | —     | —              | 0.163 (0.070, 0.277)      |
| RUVC_plasma              | 0.679   | 0.108  | —     | —              | 0.664 (0.489, 0.900)      |
| RUVC_CSF                 | 1.19    | 0.125  | —     | —              | 1.15 (0.941, 1.391)       |
| Lambda_plasma            | 0.280   | 0.107  | —     | —              | 0.275 (0.064, 0.482)      |
| Lambda_CSF               | 0.285   | 0.107  | —     | —              | 0.279 (0.066, 0.485)      |
| Delta_plasma             | −0.174  | 0.052  | —     | —              | −0.178 (−0.287, −0.063)   |

SE, standard error from NONMEM covariance step; CV, coefficient of variation; IIV, between-subject variability; Cov, covariance; RUV, residual error; θ, estimated covariate effect.

Lambda and delta are parameters from the dynamic-transform-both-side approach for residual error modelling (more specifically, lambda is the shape parameter and delta is the scedasticity parameter; together they are a part of the Box-Cox power parameter, \( zeta = lambda + delta \)).

aIndicates that the value is on the logit scale.

Figure 2. Basic goodness-of-fit plots for the final model. The top two plots show observed concentration (DV) versus population predictions (PRED) for plasma and CSF samples. The bottom two plots show CWRES versus time after dose (TAD) for plasma and CSF samples.
Figure 3. Visual predictive check showing the 2.5th, 50th and 97.5th percentiles of the observed data (lines and open circles) compared with the 95% CIs of the corresponding simulations from the final model (shaded areas). The top panel shows plasma and CSF for NeoMero-1 and the bottom panel shows plasma and CSF for NeoMero-2.

Figure 4. Box-and-whisker plots of the probability of treatment failure versus $C_{\text{min}}$/MIC (left) and $AUC_{0-24}$/MIC (right) ratios for the LOS patients with Gram-negative organisms and corresponding meropenem MIC. Open circles represent the raw data for each patient and filled circles represent patients who died.
are in agreement with what has been previously reported in the literature. For example, van den Anker et al. found that CL was 0.43 L/h and V was 0.97 L for a population of premature and mature infants. When only premature infants with an approximate weight of 1 kg were studied, the CL was lower, specifically 0.06 L/h and 0.15 L/h. A lower clearance of 0.13 L/h was also reported by Smith et al.; however, in all these cases the infants weighed around 1 kg, which would explain the lower CL estimate. This is also the reason for a 12-hourly frequency to be retained in the youngest premature age group.

Since meropenem showed low potential for nephrotoxicity, higher doses do not necessarily mean increased toxicity. Therefore, if needed, the doses could be increased or meropenem could be given more frequently.

Conclusions

A PK model describing plasma and CSF meropenem data in young infants with confirmed or suspected LOS and/or meningitis was developed using data from one of the largest infant sepsis trials to have been conducted in this population. Dosing of 20 mg/kg as an 8-hourly bolus may be adequate for LOS at current MIC targets, but in future 40 mg/kg may be necessary owing to increasing pathogen MICs. Increasing infusion times (up to continuous infusion) improves circulating %T>MIC, but decreases CSF %T>MIC.

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Members of the NeoMero Consortium

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Transparency declarations

None to declare.

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