Clinical Pharmacology Review

NDA	22056/S-018
Submission Date	4/3/2015
Brand Name	Prilosec
Generic name	omeprazole
Type/Category	Proton-pump inhibitor
Dosage Form and Strength	Oral Capsules, Oral Suspension
Route of Administration	Oral
Proposed Indication	Healing of Erosive Esophagitis
Applicant	AstraZeneca
OND Division	DGIEP
OCP Division	DCP 3
Clinical Pharmacology Primary Reviewer	Dilara Jappar, PhD
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Pharmacometrics Primary Reviewer	Justin Earp, PhD
Pharmacometrics Secondary Reviewer (or Team Leader)	Nitin Mehrotra, PhD

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1. Executive Summary

1.1. Recommendations

The Division of Pharmacometrics and Office of Clinical Pharmacology have reviewed this application and found the applicant's proposed dosing regimen to be acceptable.

1.2. Recommended PMR and/or PMC

No post-marketing requirements or commitments are necessary for NDA 22056/S-18 from a Clinical Pharmacology perspective.

1.3 Summary of Clinical Pharmacology Findings

Omeprazole (Prilosec) is approved in the US for the treatment of GERD and the maintenance of healing of erosive esophagitis in adults and children 1 – 16 years of age. With this submission, the applicant is seeking to fulfill a PREA requirement with regards to children 1 month to 1 years of age. Exposure response relationships have been established for time that intragastric pH is greater than 4 for both pediatrics and adults and these relationships are comparable. Based on this observation and results from the December 5th, 2010 GIDAC meeting on PPIs in infants, an exposure matching approach has been taken to select doses and support approval in infants for the treatment of erosive esophagitis due to acid mediated gastroesophageal reflux disease (GERD). The applicant has proposed doses of 2.5, 5, and 10 mg in an oral suspension formulation for children weight 3-5 kg, 5-10 kg, or 10-20 kg respectively (~0.5-1.0 mg/kg). Exposures in each of these groups appear to be comparable to either that in adults after a 20 mg dose or those in in children 1 – 16 years of age with the approved dose. Additionally, safety data from Study 251 at a dose of 1.5 mg/kg would suggest that the safety profile is well tolerated at exposures higher than what are expected from the proposed dosing regimen. Thus, the applicant's proposed dosing regimen appears reasonable.

2. Question-Based Review (QBR)

2.0. Key Review Questions

2.0.1. What is the pertinent regulatory background?

Omeprazole (Prilosec) is approved in the US for the treatment of GERD and the maintenance of healing of erosive esophagitis in adults and children 1 – 16 years of age. With this submission, the applicant is seeking to fulfill a PREA requirement with regards to children 1 month to 1 years of age.

In February of 2014 the FDA informed the Applicant:

> **"Your proposal to use available PK/PD and safety data from previous studies with omeprazole in children to fulfill a bridging strategy (and therefore determine appropriate dosing) may be an acceptable option to fulfill the PMR. However, whether the PMR is fulfilled is a review issue, especially since we do not know whether the PK/PD and safety data that you plan to submit will be sufficient.**
>
> **Clarify what omeprazole PK and PD data you intend to use in this PK/PD analysis. As a general note, in order to use an exposure matching strategy to extrapolate the efficacy from adult to pediatric patients aged 1 month to 11 months, you should demonstrate a similar exposure-response relationship for omeprazole between adults and pediatric patients aged 1 month to 11 months.**
>
> **Please include your rationale for extrapolation in your submission."**

The applicant is submitting the following data to fulfill the PMR.

- PK/PD relationship in both children and in adults:

- Population PK modeling assessment in small children

- Proposed doses in children giving an exposure in children similar to the exposure in adults given the EE dose (20 mg).

Below is further text from the Applicant highlighting the regulatory history of this product in pediatrics less than 1 year of age.

On March 15, 2012, [redacted] (b) (4) the post marketing requirement (PMR) for Prilosec (omeprazole magnesium) for Delayed Release Oral

Suspension-1396-1 Deferred pediatric study under PREA for the treatment of Gastrointestinal Esophageal Reflux Disease (GERD) and Erosive Esophagitis (EE) in pediatric patients ages birth to one year. [redacted] (b) (4)

On October 10, 2013, FDA released AstraZeneca from the PMR. FDA determined the release of the PMR was due to the following reasons: (i) studies would be impossible or highly impractical in patients aged birth to < 1 month with GERD and EE; (ii) there is evidence that PPIs, like Prilosec, are not effective for the treatment of symptomatic GERD in patients < 1 year of age; and (iii) the above PREA PMR will be replaced by the new PREA PMR for patients aged 1 month to 11 months, with EE as agreed upon in the AstraZeneca e-mail dated June 20, 2013. New PMR: 2062-1 Deferred study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of omeprazole in patients 1 month to 11 months of age with erosive esophagitis (EE).

Final Protocol Submission: March 2014

Study/Trial Completion: March 2016

Final Report Submission: September 2016

In the June 20, 2013 e-mail Astra Zeneca noted that we still have concerns that recruitment for even this study may be extremely difficult if not impossible and we may be requesting FDA feedback regarding the proposed study once we have completed feasibility.

On December 20 AstraZeneca, after completed the feasibility, submitted a report to the FDA where AZ concluded that the new PMR required study would be impossible or highly impracticable to conduct. Further, it could be discussed if it would be ethical to justify the risks of such an invasive study in small children as the studied therapy would not represent a meaningful benefit over already existing therapies.

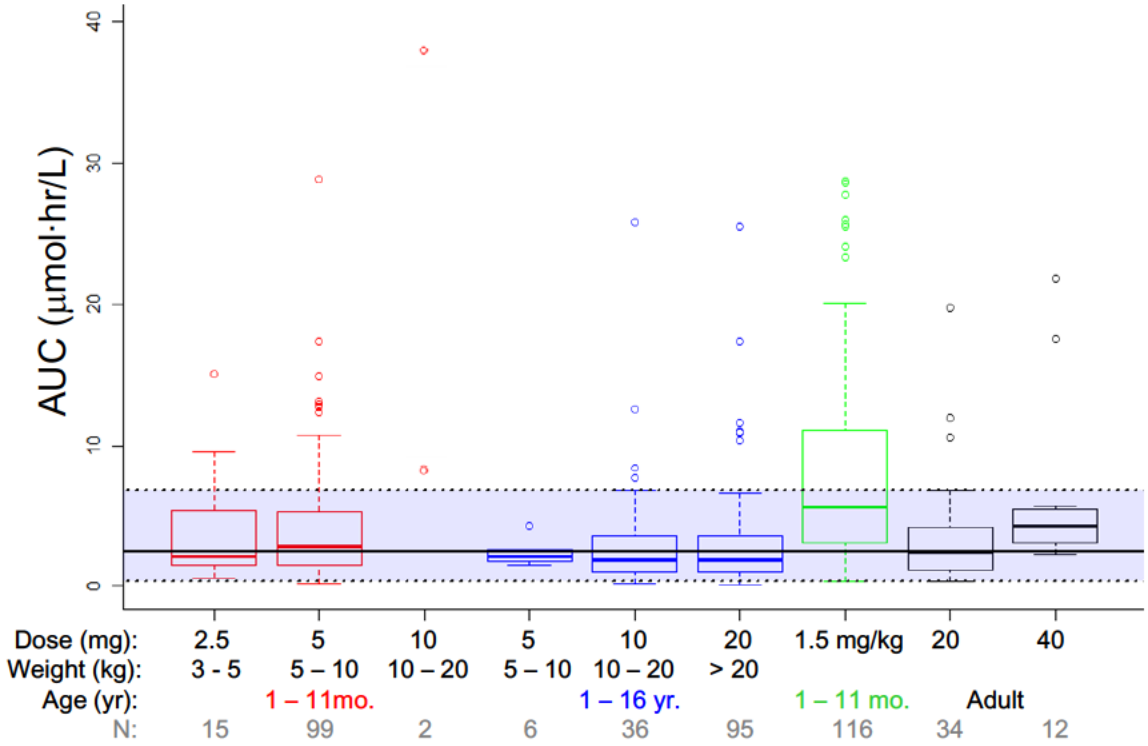
AstraZeneca has previously conducted several pediatric studies with omeprazole, also including infants aged 1-11 months. With this complementary document we now submit a PK/PD analysis report and supportive safety data that provides the evidence that we believe validates appropriate doses of omeprazole for the indication erosive esophagitis in children 1 month to 11 months of age.

2.0.2. Is the proposed dosing regimen in infants acceptable?

Yes, simulated exposures for the proposed dosing regimen appear to match those from adults and those from the approved doses in children 1 -16 years of age (Figure 1). Exposures were predicted based on the population PK model in pediatrics 1 month to 16 years of age for data from 253 pediatric subjects in three studies (245, 250, and I-678). This comparison was also made by the applicant for C_{max} values and is described further in Part II, Section 3 with the same

conclusion. It should be noted that PK data were only available from four infants less than 1 year of age. However, PK variability defined across all pediatrics was used in combination with the database of demographics of infants with the final population PK covariate model to simulate the anticipated range of exposures for the proposed dosing regimen. Additionally, the projected exposures do not exceed those expected for a dose of 1.5 mg/kg (green box, Figure 1). This dose was studied in Study 251, however, while PK data was not available from this study, there is safety data available for this higher dose which is being used to inform safety in 1-11 month pediatric population. See the medical review by Dr. Marjorie Dannis in DAARTs dated 12/26/2015 for further safety details.

Figure 1. Omeprazole AUC after simulation at the proposed dosing regimen in infants (red boxes) appears to match exposures from the adult 20 mg regimen (left of the black boxes).



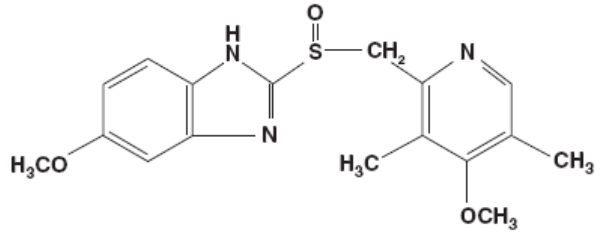
The exposure matching approach was deemed acceptable after prior discussions with the agency (see Section 2.0.1) based on results of the December 5, 2010 GIDAC meeting and is supported by the finding of a similar PK/PD relationship between infants less than 2 years of age and adults (see Section 3.1 of the Pharmacometric Review for further details). This similar relationship suggests that therapeutic concentrations in infants are the same as those in adults with the approved dose.

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance or therapeutic protein and the formulation of the drug product as they relate to clinical pharmacology review?

Drug Substance: The empirical formula for omeprazole is: C17H19N3O3S, with a molecular weight of 345.42

Figure 1: Structure of Dexlansoprazole



Formulation:
The formulation for the pediatric studies where PK data were collected (Study 245, 250, I-678) was the contents of the oral capsule suspended in an aqueous 8.4% sodium bicarbonate solution. This method of administration is consistent with the current approved US label for omeprazole, dated 12/19/2014.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Omeprazole is a proton pump inhibitor indicated for the treatment of GERD and maintenance of healing of erosive esophagitis in pediatrics 1 year to (b) (4) adults. In this submission, the applicant is seeking approval of omeprazole for the healing of erosive esophagitis in infants 1 months to less than 1 year old.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The product is an oral suspension. The proposed doses for infants less than 1 year old are 2.5, 5, and 10 mg for infants weight 3-5 kg, 5 – 10 kg, or 10-20 kg respectively.

2.2. General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Study 245

Study 245 was a PK study of omeprazole following single and repeated daily oral dose administration of omeprazole in 36 healthy children of 2-16 years of age. Doses were 10 mg omeprazole for children less than 20 kg, and 20 mg omeprazole, for those greater than 20 kg administered as a capsule. Only the PK data from the repeated dose were used in this analysis.

Study 250

Study 250 was initially designed as a PK study for single and repeated daily oral dose of omeprazole in pediatric subjects of 0-24 months, inclusive. The study was later amended to a PK study only for a single omeprazole dose due to the difficulty in enrolling

sufficient number of subjects. The doses were 0.5, 1.0 and 1.5 mg/kg. Of 25 subjects, only four subjects had the repeated PK data and were included in this population PK modeling analysis.

Study I-678

Study I-678 was an open label, dose-finding study to evaluate the omeprazole safety and efficacy in children of 2-16 year-olds with reflux esophagitis. Omeprazole concentrations were determined in 25 subjects following repeated daily oral dose administration of omeprazole. The starting dose for each subject was 0.7 mg/kg. The dose was increased by 0.7 mg/kg every 5-14 days until the esophageal pH was below 4 for ≤ 6% of 24 hours dose interval. Due to varying weight among subjects, the resulting absolute dose administration ranged from 7.5 to 80 mg. One subject was excluded from the population PK modeling analysis due to the co-administration of phenobarbital, a well-known inducer of drug metabolism.

2.2.2 What is the basis for selecting the response endpoints [i.e., clinical or surrogate endpoints or biomarkers (collectively called PD)] for dose selection and how are they measured in clinical pharmacology and clinical studies?

The response endpoints are measures of intragastric pH (i.e. time above intragastric pH 4 and average intragastric pH within the first 24 hours post dose). These are are common PD biomarkers used across the class of proton pump inhibitors. The approval basis for infants 1 month to 1 year old is supported by exposurematching infant exposures to those in adults to select the dose. This approach was deemed reasonable based on the results of the GIDAC meeting on December 5, 2010 which discussed approval of PPIs in pediatrics less than 1 year of age.

2.2.3 Are the active moieties (parent drug and relevant metabolites) in the plasma (or other biological fluids) appropriately identified and measured to assess PK parameters and exposure-response relationships?

Yes, Please refer to section 2.6, analytical section.

2.2.4 Exposure-response (Refer to guidance – *Exposure-Response Relationships*: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm)

2.2.4.1 What are the characteristics of the exposure-response (E-R) relationships (dose-response, concentration-response) for pharmacological effects and *efficacy*? Is the relationship steep or flat? What are the onset and offset times of therapeutic and pharmacological effects?

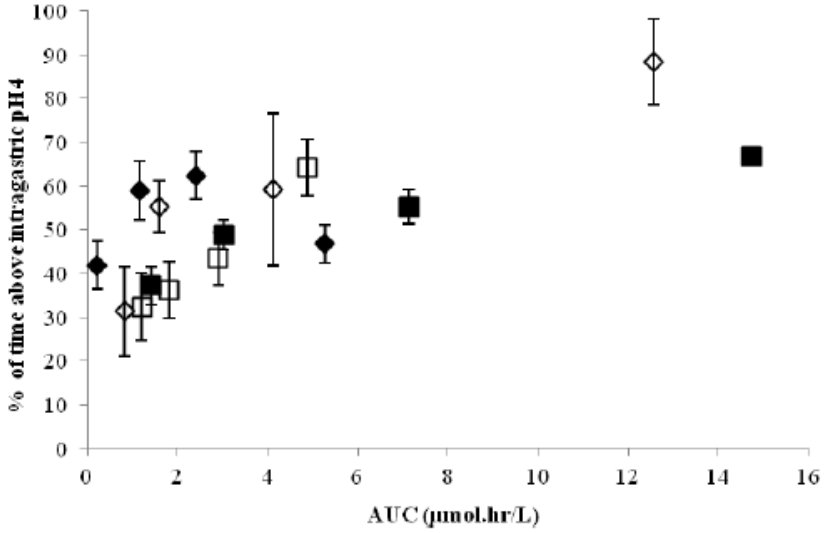
The applicant plotted an exposure response assessment for both pediatrics and adults and for both omeprazole and esomeprazole in Figure 2.

"The surrogate endpoint for omeprazole/esomeprazole effect was "% of time above intragastric pH4". The AUCs from each respective study were divided into 4 exposure quartiles and the

median AUCs were graphically compared to the mean "% of time above intragastric pH4" (Figure 2).

The omeprazole and esomeprazole exposure-response appears to be similar between adults and children. Together with the consensus of the GIDAC-meeting about the appropriateness of extrapolating the exposure-response relationship between adults and children for PPI's in treatment of erosive esophagitis, the matching of omeprazole exposure between adult and pediatric populations were thus deemed feasible for dose justifications."

Figure 2. Exposure-response relationship for omeprazole (open symbols) and esomeprazole (closed symbols) in adult (squares) and pediatric subjects (diamonds). Each group of subjects represented by median AUC and mean % time above intragastric pH 4 (mean ± SE). For the omeprazole, there were PD data from 14 pediatric subjects 4.5 – 27 months of age and 36 adults. For esomeprazole PD data were available from 52 neonates and infants and 52 adults.



(Source: Applicant's Response to PMR Document, Figure 1)

2.2.4.2 What are the characteristics of the E-R relationships (dose-response, concentration-response) for *safety*? Is the relationship steep or flat? Are the exposure-efficacy and exposure-safety relationships clearly separated?

No exposure-response for safety has been established since PK data was only available from 4 infants one month to 1 year of age. Omeprazole's safety profile is generally well tolerated. See the medical review by Dr. Marjorie Dannis in DARRTS for more details.

2.2.4.3 Is the dose and/or dosing regimen selected by the sponsor consistent with the known E-R relationship? Is there a need for individualized dosing or is "one-size-fits-all" dosing regimen acceptable based on the exposure-response relationship? Are there any unresolved dosing or administration issues?

Yes, exposures (AUC) with the proposed doses in pediatrics are similar to adult exposures with the approved dose and fall into the plateau of the PK/PD relationship (Figure 2). See the pharmacometric review for further details.

2.3. Intrinsic Factors

2.3.1 What intrinsic factors influence exposure (PK of parent and/or relevant metabolites) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The pharmacokinetics of omeprazole in children are influenced primarily by body weight (all ages) and age (for infants less than one year). The range of effect of age on clearance is a factor of ~0. At 1 month and a factor of 1.0 at 1 year and above. Body weight is allometrically scaled for both clearance (coefficient = 0.75) and volume of distribution (coefficient = 1.0). The dose selection in pediatrics is based on matching exposures with adults at the approved dose.

See the Pharmacometrics Review (Part 2) for further details.

2.5 General Biopharmaceutics

How does the formulation used in this NDA submission compare to those approved previously?

The formulation used in the studies relevant for this submission is previously approved. See Section 2.1.1 for further details.

2.6 Analytical section

In the population PK analysis, the sponsor had utilized the PK data form three studies, study 245, study 250 and study I-678 in their analysis.
Plasma concentrations of omeprazole in studies 245 and 250 were determined at (b) (4) using liquid chromatography with MS/MS detection (LC/MS/MS) according to methods number HL 18618_2 and HL 18618_3, respectively with a limit of quantitation of 5.0 ng/mL. Plasma concentrations of omeprazole in study I-678 were determined at (b) (4) using liquid chromatography according to the method reported by Lagerström et al. (Lagerstöm 1984).

Studies 245 and 250 have previously been reviewed and found to be acceptable by the agency. Since bioanalytical method validation and in study bioanalytical report for study I-678 have not been submitted and reviewed by the agency previously, this review will focus on the bioanalytical method utilized in study I-678. Overall, the bioanalytical method utilized in study I-678 appears to be acceptable.

Bioanalytical Method of Study I-678:
Following the PK blood sampling in study I-678, the samples were kept at room temperature for at least 5 min and then centrifuged for 10 min. The plasma phase was then transferred to plastic tubes and stored at -20° C.

- Plasma concentrations of omeprazole in human plasma were measured by a validated liquid chromatographic method with UV detector at Bioanalytical Chemistry, Astra Hässle. This bioanalytical method was developed and validated at (b) (4).

- Precision, measured as the inter-assay percent coefficients of variation (CV%) of the QC was evaluated at concentrations close to 2800 and 2900 nmol/L and it ranged from 04% - 5.7%. Accuracy, expressed as the mean percent differences from theoretical ranging was evaluated at concentrations close to 1450nmol/L from -7.9% to 3.3%.

- Calibration standard curve consisted of 7 concentration levels and was linear between tested ranged of 25 to 25000 nmol/L in human plasma.

- The differences of back-calculated calibration curve values from nominal values ranged from 0.3% to 9.4%.

- Plasma samples were stored at approximately -18^{o}C until analysis. Plasma samples were analyzed within acceptable time period for which long-term stability of plasma omeprazole was established.
    - Patients were enrolled in the study between 04-30- 1994 and 11- 22- 1995.
    - Frozen samples were arrived at the bioanalytical site between 03-29-1995 and 12-09-1995 and were stored at -18^{o}C until analysis.
    - Plasma samples were analyzed between 06-16-1995 through 1-26-1996 (with specific dates of 06-16-1995, 06-20-1995, 11-09-1995, 01-09-1996, 01-26-1996)
    - The long term storage stability of omeprazole in human plasma at -18 °C was established for at least for one year (365 days).
    - Plasma omeprazole stability at -20^{o}C was established for 449 days in NDA 22511.

Bioanalytical method Validation:
This bioanalytical method of measuring the concentration of omeprazole by liquid chromatographic method was validated at (b) (4).

- Linearity: Calibration standard curve consisted of 7 levels and it was linear at concentration ranged from 25 to 25000 nmol/L in human plasma, with an LLOQ of 25 nmol/mL,

- LLOQ: Lower limit of quantification was nominally was 25 nmol/mL

- Stability:

freeze-thaw	room temperature at 25^{o}C	at -18°C
3 cycles	4 days	One year at least

- Selectivity: The bioanalytical method was selective toward omeprazole that omeprazole is separated from the identified and potential metabolites.

- Precision and Accuracy: Reproducibility was assessed by analyzing identical plasma samples at omeprazole concentration of 2-6 umol/L, 2 samples a day, during two to three month period. CV% was 3.1-4.5% and was and mean percent differences from theoretical ranging from ranged from -1% to 4%.
  Between-day precision was evaluated at 1500 nmol/L and was between 0.6-0.9%.

3 Detailed Labeling Recommendations

At the time of this review, labeling recommendations have not been finalized. An addendum to this review will document the final labeling recommendations and reference this review document.

Part II: Supporting Material – Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

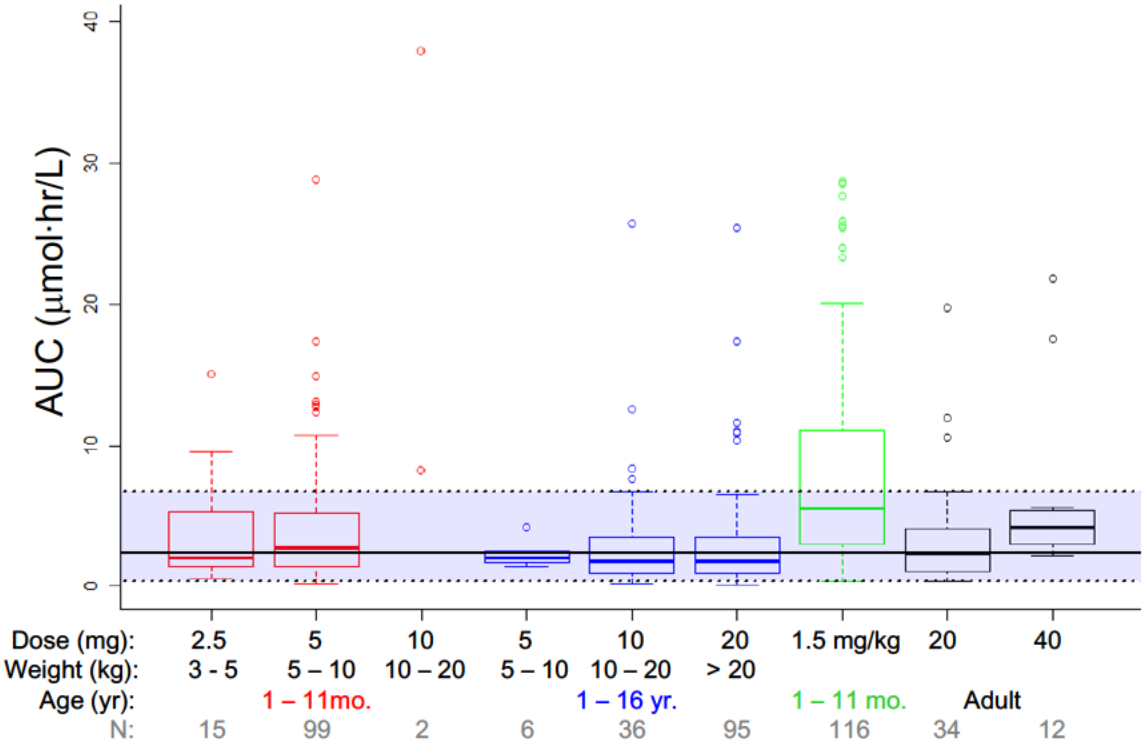
1 SUMMARY OF FINDINGS

1.1 Key Review Questions

1.1.1 Is the proposed dosing regimen in infants acceptable?

Yes, simulated exposures for the proposed dosing regimen appear to match those from adults and those from the approved doses in children 1 -16 years of age (Figure 1). Exposures were predicted based on the population PK model in pediatrics 1 month to 16 years of age for data from 253 pediatric subjects in three studies (245, 250, and I-678). It should be noted that PK data were only available from four infants less than 1 year of age. However, PK variability defined across all pediatrics was used in combination with the database of demographics of infants with the final population PK covariate model to simulate the anticipated range of exposures for the proposed dosing regimen. Additionally, the projected exposures do not exceed those expected for a dose of 1.5 mg/kg (green box, Figure 1). This dose was studied in Study 251, however, while PK data was not available from this study, there is safety data available for this higher dose which is being used to inform safety in 1-11 month pediatric population. See the medical review by Dr. Marjorie Dannis in DAARTs dated 12/26/2015 for further safety details.

Figure 1. Omeprazole AUC after simulation at the proposed dosing regimen in infants (red boxes) appears to match exposures from the adult 20 mg regimen (left of the black boxes).



The exposure matching approach was deemed acceptable after prior discussions with the agency (see Section 2), based on results of the December 5, 2010 GIDAC meeting and is supported by the finding of a similar PK/PD relationship between infants less than 2 years of age and adults (see Section 3.1 for further details). This similar relationship suggests that therapeutic concentrations in infants are the same as those in achieved in adults with the approved dose.

1.2 Recommendations

The Division of Pharmacometrics, Office of Clinical Pharmacology has reviewed this application and found the applicant's proposed dosing regimen to be acceptable and recommend approval of the pediatric efficacy supplement.

2 PERTINENT REGULATORY BACKGROUND

Omeprazole (Prilosec) is approved in the US for the treatment of GERD and the maintenance of healing of erosive esophagitis in adults and children 1 – 16 years of age. With this submission, the applicant is seeking to fulfill a PREA requirement with regards to children 1 month to 1 years of age.

In February of 2014 the FDA informed the Applicant:

> **"Your proposal to use available PK/PD and safety data from previous studies with omeprazole in children to fulfill a bridging strategy (and therefore determine appropriate dosing) may be an acceptable option to fulfill the PMR. However,**

whether the PMR is fulfilled is a review issue, especially since we do not know whether the PK/PD and safety data that you plan to submit will be sufficient.

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Please include your rationale for extrapolation in your submission."

The applicant is submitting the following data to fulfill the PMR.

- PK/PD relationship in both children and in adults:

- Population PK modeling assessment in small children

- Proposed doses in children giving an exposure in children similar to the exposure in adults given the EE dose (20 mg).

Below is further text from the Applicant highlighting the regulatory history of this product in pediatrics less than 1 year of age.

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AstraZeneca has previously conducted several pediatric studies with omeprazole, also including infants aged 1-11 months (see the Clinical safety report). With this complementary document we now submit a PK/PD analysis report and supportive safety data that provides the evidence that we believe validates appropriate doses of omeprazole for the indication erosive esophagitis in children 1 month to 11 months of age.

3 RESULTS OF SPONSOR'S ANALYSIS

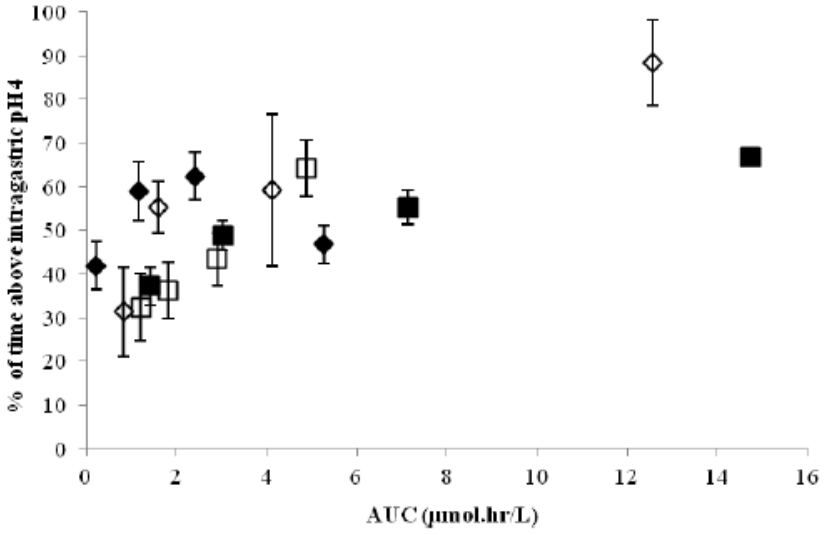
3.1 PK/PD Data Support Exposure Matching

The applicant plotted an exposure response assessment for both pediatrics and adults and for both omeprazole and esomeprazole in Figure 2.

"The surrogate endpoint for omeprazole/esomeprazole effect was "% of time above intragastric pH4". The AUCs from each respective study were divided into 4 exposure quartiles and the median AUCs were graphically compared to the mean "% of time above intragastric pH4" (Figure 1).

The omeprazole and esomeprazole exposure-response appears to be similar between adults and children. Together with the consensus of the GIDAC-meeting about the appropriateness of extrapolating the exposure-response relationship between adults and children for PPI's in treatment of erosive esophagitis, the matching of omeprazole exposure between adult and pediatric populations were thus deemed feasible for dose justifications."

Figure 2. Exposure-response relationship for omeprazole (open symbols) and esomeprazole (closed symbols) in adult (squares) and pediatric subjects (diamonds) months of age. Each group of subjects represented by median AUC and mean % time above intragastric pH 4 (mean ± SE). For the omeprazole, there were PD data from 14 pediatric subjects 4.5 – 27 months of age and 36 adults. For esomeprazole PD data were available from 52 neonates and infants and 52 adults.



(Source: Applicant's Response to PMR Document, Figure 1)

Reviewer's Comments:

While the exposure response relationship may not be identical between the two different molecules, it does appear to overlap between children (one month to 2 years of age for omeprazole and one month to 1 year of age for esomeprazole) and adults for both omeprazole and esomeprazole. Considering that these molecules share the same mechanism of action, it is reasonable to conclude that matching omeprazole exposures in pediatrics to adult exposures is appropriate for dose selection in infants one month to 1 year of age.

3.2 Pediatric Omeprazole Population PK Model

Data from repeated daily administration was used throughout this analysis due to the time dependent change in PK shown by omeprazole. The population PK analysis was based on AstraZeneca in-house studies: 245, 250 and I-678, detailed descriptions of the number of subjects, ranges of dose and age, plasma sampling schedule and number of concentration data available in each study are shown in Table 1 and the studies are described in brief below.

Study 245

Study 245 was a PK study of omeprazole following single and repeated daily oral dose administration of omeprazole in 36 healthy children of 2-16 years of age. Doses were 10 mg omeprazole for children less than 20 kg, and 20 mg omeprazole, for those greater than 20 kg administered as a capsule. Only the PK data from the repeated dose were used in this analysis.

Study 250

Study 250 was initially designed as a PK study for single and repeated daily oral dose of omeprazole in pediatric subjects of 0-24 months, inclusive. The study was later amended to a PK study only for a single omeprazole dose due to the difficulty in enrolling sufficient number of subjects. The doses were 0.5, 1.0 and 1.5 mg/kg. Of 25 subjects, only four subjects had the repeated PK data and were included in this population PK modeling analysis.

Study I-678

Study I-678 was an open label, dose-finding study to evaluate the omeprazole safety and efficacy in children of 2-16 year-olds with reflux esophagitis. Omeprazole concentrations were determined in 25 subjects following repeated daily oral dose administration of omeprazole. The starting dose for each subject was 0.7 mg/kg. The dose was increased by 0.7 mg/kg every 5-14 days until the esophageal pH was below 4 for $\leq$ 6% of 24 hours dose interval. Due to varying weight among subjects, the resulting absolute dose administration ranged from 7.5 to 80 mg. One subject was excluded from the population PK modeling analysis due to the co-administration of phenobarbital, a well-known inducer of drug metabolism.

A description of the blood sampling schedule for each study and samples available are outlined in Table 1.

Table 1 Studies and blood samples used in population PK modeling analysis.

Study	N	Age range	Dose	Blood sampling schedule	Number of omeprazole plasma concentration measurements available for analysis
245	36	2-16 years	10/20 mg	0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours	225
250	4	0.5-4.2 months	2.4-10.5 mg	0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours	23
I-678	24	1.6-12.8 years	7.5-80 mg	0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours	139
All	64	0.5 months -16 years	2.4-80 mg	0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours	387

Limit of quantitation of omeprazole plasma concentration: I-678, 8.6 ng/ml; Other studies, 5 ng/ml

(Source: Applicant's Response to PMR Document, Table 1)

To determine the effect of age on clearance the applicant sought additional data from the literature:

Faure et al. reported the clearance following repeated iv infusions of omeprazole in 9 children aged from 4.5 to 27 months (Faure 2001). The omeprazole plasma concentration data following iv infusion in 25 pediatric subjects aged from 8 days to 13 months were also available from Östra Hospital in Göteborg, Sweden. Omeprazole PK from eight of those subjects was reported previously by Andersson et al (Andersson 2001). These subjects were under treatment for a variety of medical conditions. A number of subject data were excluded for a variety of reasons[1]. The remaining data in 21 subjects (one subject was counted two times, 104 and 107, respectively), together with the 9 subjects from Faure' study, were analyzed to explore the age effect on omeprazole clearance and volume of distribution approximately from birth to toddlers.

In summary, the final full covariate model was a one-compartment model with 1st order absorption with a lag-time implemented as a series of transit compartments. CL/F and V/F were scaled allometrically by body weight, with the exponents fixed to 0.75 and 1 respectively. Age was found to be a significant covariate for CL/F, and the parameters describing the age relationship, CLAGE and KCLAGE, were fixed based on the estimates from the iv data. Inter-individual variability was estimated for CL/F, V/F and ka. Residual error variability was described by both an additive and proportional residual error model.

[1] Subject 101 was excluded from the analysis because of concomitant medication with fluconazole, a well-known inhibitor of the metabolism of many drugs. One subject had two occasions of omeprazole treatment, at 10 days and 7 months of age. Since significant developmental changes occurred between the two treatments, the omeprazole concentration measurements at the two different ages were treated as if they were from two different subjects, labeled as subjects 104 and 107 respectively in the Table 2. Another subject (106 or 108) also had two occasions of omeprazole treatment, at 13.5 and 17 months, respectively. Since the age and body weight spans across the two occasions of omeprazole treatment are fairly close, the omeprazole treatment at 17 months (labeled subject 108) in Table 2 was not used in the data analysis. In addition, subjects 118 and 123 were also excluded from the data analysis due to unknown status of the steady state.

Final parameter estimates are shown in Table 2. Plots of the observed, predicted/individual predicted concentrations of omeprazole are shown in Figure 3. Plots of the predictions vs observed over time for the 4 infants from study 250 are shown in Figure 4.

Shrinkage for CL/F, V/F and ka were estimated to be 6.09%, 6.45% and 22.4% respectively.

The age effect on CL following iv administration of omeprazole could adequately be described with the applied maturation function. CL_{AGE} was estimated to be 0.649 (%RSE 33.7) and KCL_{AGE} at 4.95 $year^{-1}$ (%RSE 84.2). The age effect was incorporated in the final model as fixed parameters and improved the overall model fit (Table 2).

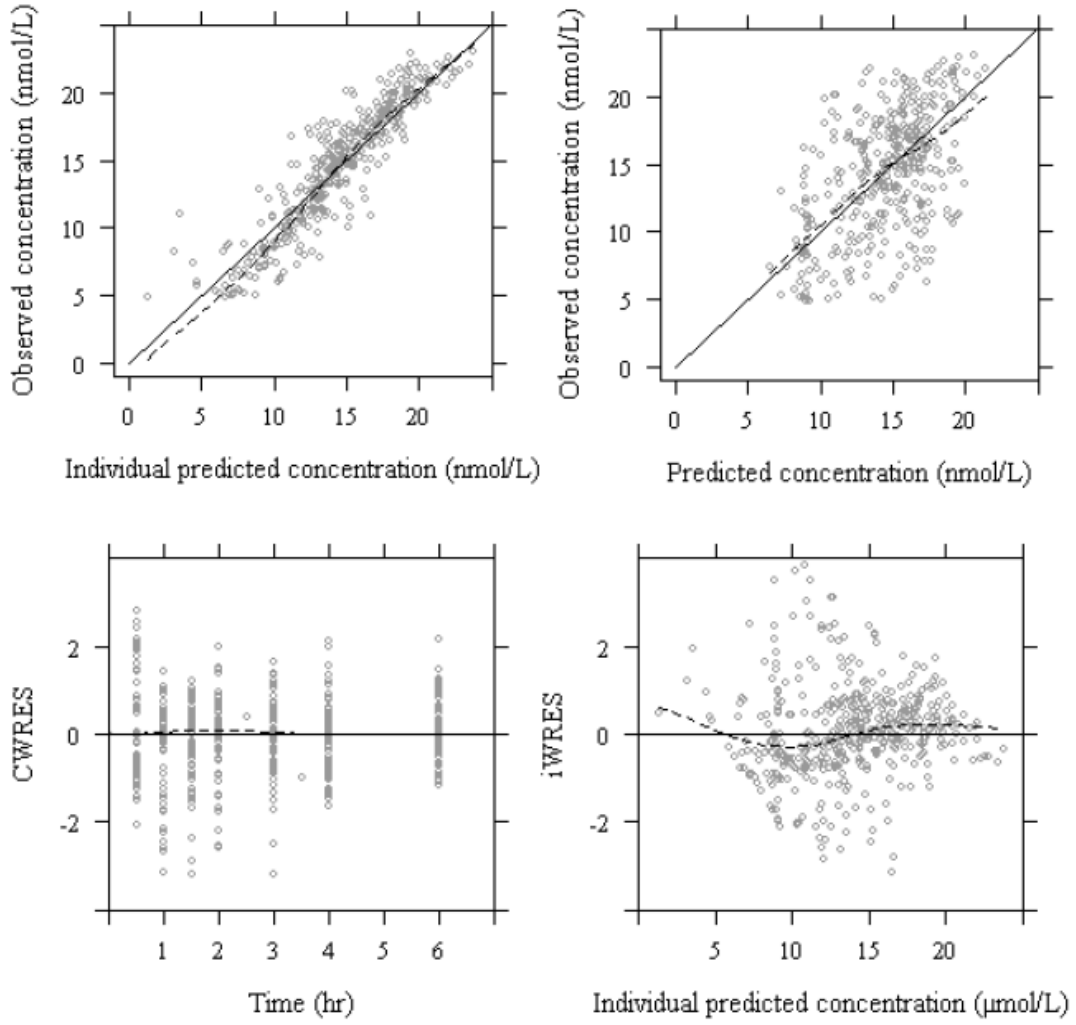
Table 2. Parameter Estimates for the Final Omeprazole Population PK Model

	Estimate (RSE)[a]	
Parameter	**Model 3**	**Bootstrap**
Ka (h^{-1})	2.43 (13.4)	2.54 (13.0)
CL/F (L/hr)	37.1 (11.2)	37.4 (13.0)
V/F (L)	64.4 (11.7)	64.2 (17.0)
MTT (hr)	0.782(8.64)	0.788 (8.77)
N	6*	6*
F_{rel}	1*	1*
Weight CL/F ($TV*(WT/70)^{\theta}$)	0.75*	0.75*
Weight V/F ($TV*(WT/70)^{\theta}$)	1*	1*
AGE CL/F [b]	0.683*,4.95*	0.683*,4.95*
IIV [c] (%) CL/F	97.0 (9.57[e])	96.0 (13.6[e])
IIV [c] (%) V/F	77.5 (17.7[e])	78.1 (20.0[e])
IIV [c] (%) ka	194 (9.96[e])	193 (21.2[e])
Residual error pro [d]	0.716 (7.87)	0.694 (7.34)
Residual error add [d]	3.87 (26.5)	3.53 (49.5)

[a] RSE, relative standard error
[b] $CL = (1 - CL_{AGE} \times e^{(1-KCL_{AGE})})$
[c] IIV, inter-individual variability
[d] Presented as parameter estimates
[e] Estimated on a variance scale
* Parameter fixed

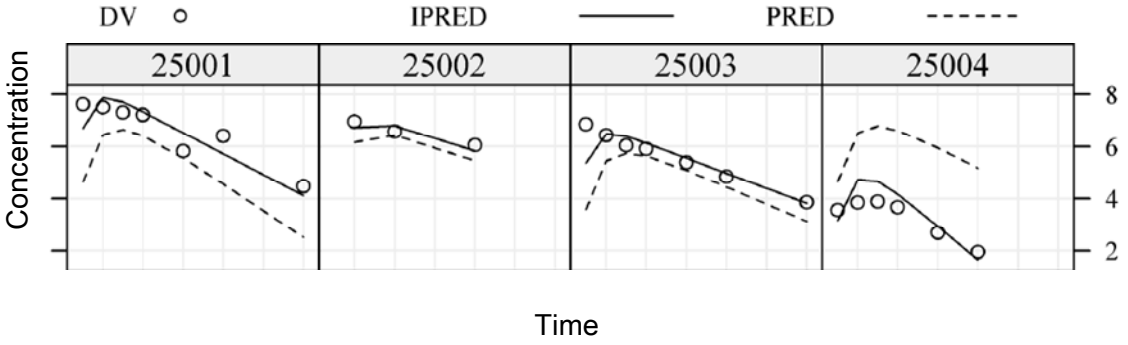
Frel indicates relative bioavailability and was fixed to one as no reference was made to PK from other formulations in the population PK model.
(Source: Applicant's Response to PMR Document, Table 6)

Figure 3. Final model diagnostic plots on log transformed data modeled in the analysis. Open circles represent the observations/predictions, dashed lines represent the LOESS smooth and solid lines represent the line of unity. Logarithmic values are plotted on a linear scale.



(Source: Applicant's Response to PMR Document, Figure 2B)

Figure 4. Individual Plots (observations/predictions vs time).



(Source: Applicant's Response to PMR Document, Appendix B)

Reviewer's Comments:

The applicant's population PK Model appears reasonable to describe the PK of infants < 1 year of age. While the data only contained PK information from 4 subjects less than 1 year of age, the applicant conducted an extensive simulation based on variability established from the entire pediatric population and the covariate relationships applied to the entire database of pediatric demographics in an effort to capture the range of potential omeprazole exposures in infants one month to < 1 year of age.

3.3 Simulations for Pediatric Dose Selection

A dataset for simulation of omeprazole exposure was composed by pooling age and weight data from 7 AstraZeneca pediatric studies of omeprazole (Studies: 245, 250 and I-678) and esomeprazole (SH-NEC-0001, SH-NEC-0002, D9614C00094, D9614C00099). Demographic data in the Östra Hospital in Göteborg, Sweden study, as well as published by Faure et al was also included (Faure 2001). The pooled dataset contained in total 297 individuals. However, in line with the purpose of this report, children below 3 kg bodyweight (n=13) and less than 1 month of age (n=31) were excluded from the simulations of omeprazole exposure. The age and weight demographics for each of the simulated dosing group, based on age and weight, are summarized in Table 3.

Table 3. Age, weight, and dosing for the simulation dataset (n=253).

1-11 months		Median body weight		Median age	
	n	(kg)	(Range)	(years)	(Range)
2.5 mg	15	3.9	(3.0-4.9)	0.19	(0.1-0.4)
5 mg	99	6.6	(5.0-9.7)	0.39	(0.1-0.8)
10 mg	2	10	(NA)*	0.68	(0.6-0.7)

1-16 years		Median body weight		Median age	
	n	(kg)	(Range)	(years)	(Range)
5 mg	6	7.9	(6.8-9.5)	1.2	(1.1-1.3)
10 mg	36	14	(10-20)	2.0	(1.0-7.0)
20 mg	95	48	(20-99)	12	(4.0-17)

*Both individuals in the dosage group had a body weight of 10 kg.

(Source: Applicant's Response to PMR Document, Figure 1)

Omeprazole exposures were simulated using the final covariate model and the age and weight-distributions from the pooled 7 studies according to the current US-label for PRILOSEC for children above 1 year and with the new proposed doses for children aged 1-11 months (Table 4). Exposures were also derived for the same doses based on the individual posthoc estimates of CL/F from the populations PK analysis and the predicted exposures based on CL (from the iv data) from the study performed at the Östra Hospital, Göteborg Sweden and data reported by Faure et al. (Faure 2001).

Table 4. Dosing Algorithm according to the current US Prilosec lable for treatment of GERD and maintenance of healing of erosive esophagitis with the recommended daily dose for pediatric patients 1-16 years of age and the proposed doses for the age range 1-11 months in present report.

US PRILOSEC label for the age group 1-16 years	
Body Weight:	Daily Omeprazole Dose
5<10 kg	5 mg
10<20 kg	10 mg
≥20 kg	20 mg

New Proposed doses for the age group 1-11 months	
Body Weight:	Daily Omeprazole Dose
3<5 kg	2.5 mg
5<10 kg	5 mg
≥10 kg	10 mg

(Source: Applicant's Response to PMR Document, Table 7)

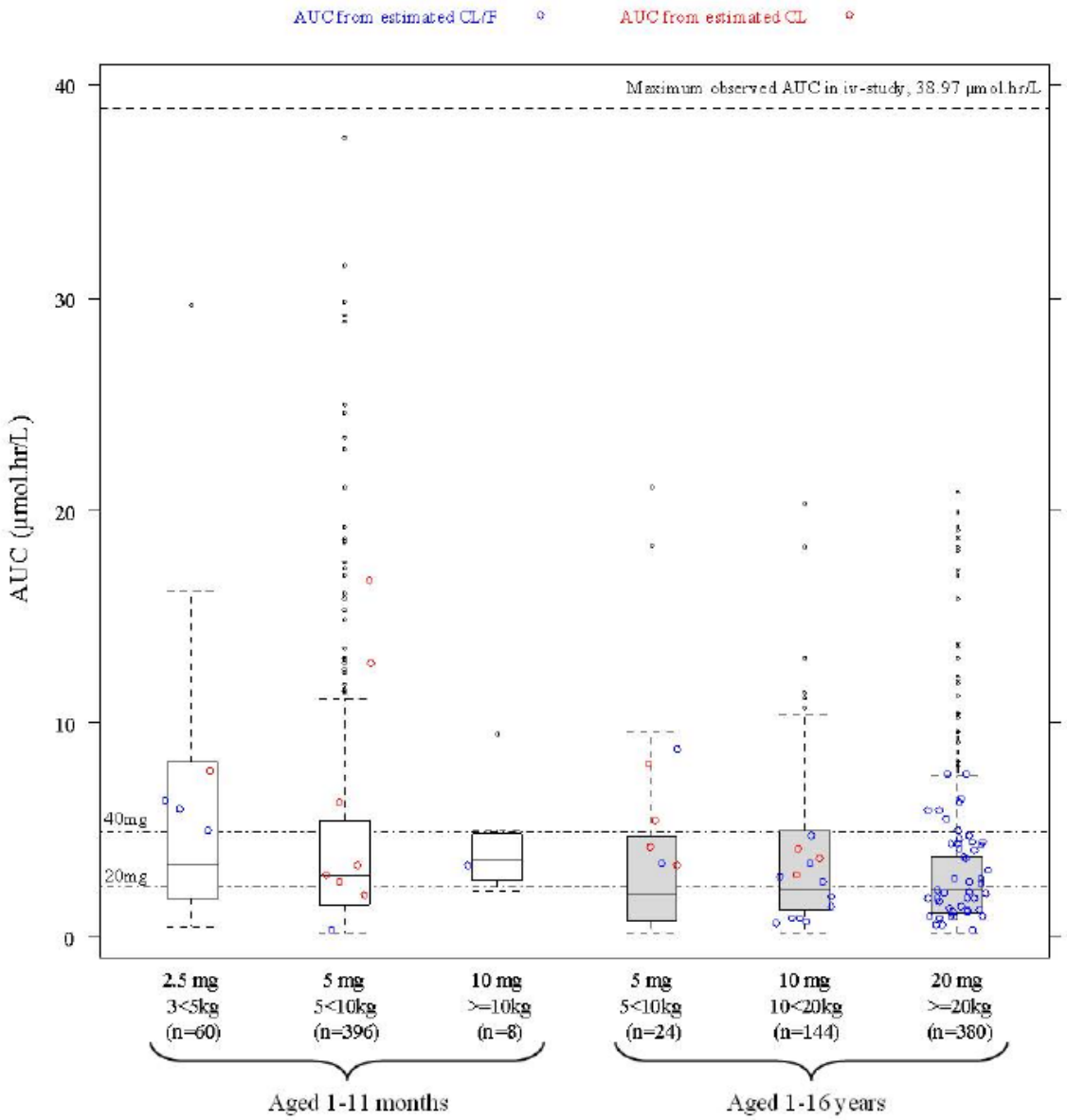
The simulated AUCs were compared to the previously observed adult exposures of 2.34 and 4.92 µmol.hr/L following treatment with either 20 or 40 mg omeprazole (AstraZeneca studies: SH-QBE-0008 and I-267). The exposure in children 1-16 years shows a good agreement with the target exposure (Figure 5). In the younger age group, 1-11 months, the observed simulated exposure was higher; however median exposure in each group were well below 4.92 µmol.hr/L (equivalent to 40 mg in adults).

The observed AUCs derived using the dosing algorithm (Table 4) and the posthoc estimates of CL/F from the studies included in the analysis dataset, or the reported iv CL values are also included in figure 5. The simulated exposure seems to be in good agreement with theses derived exposures.

An AUC of 38.97 µmol.hr/L has previously been observed in the pediatric study performed at the Östra Hospital, Göteborg, Sweden following iv infusion of omeprazole. There were no observed drug-related side effects despite this high exposure. The simulated exposures based on the proposed pediatric dosing algorithm were assessed relative to this exposure, and only 0.4% (4 out of 1012) of the simulated AUCs were above 38.97 µmol.hr/L (Figure 5). These four simulated AUCs were excluded in figure 5.

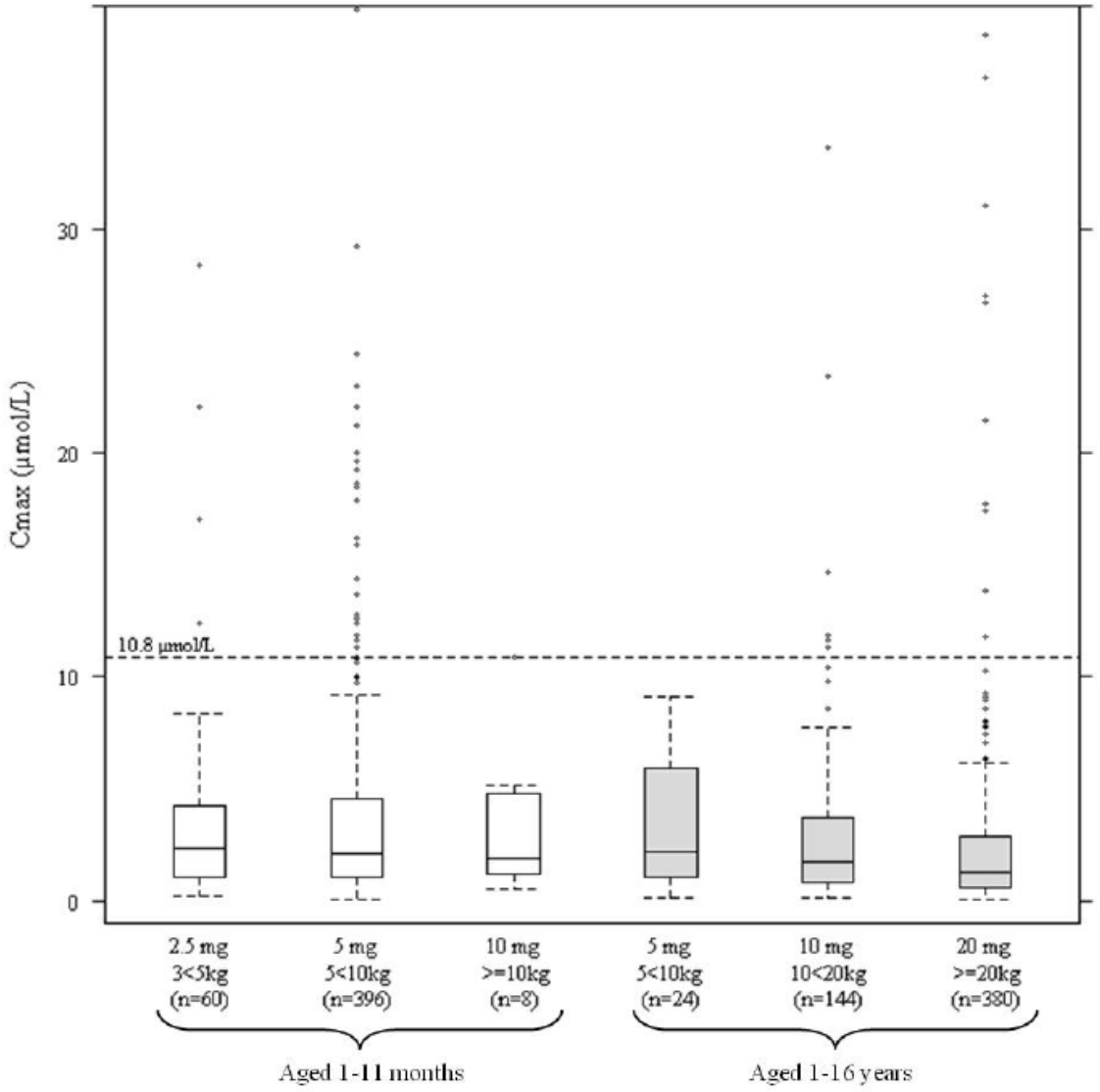
The simulated maximum omeprazole plasma concentration (C_{max}) was assessed relative to previous observations in pediatric patients (Figure 6). Some simulated C_{max}-values (n=17) were excluded in Figure 6, these were above 40 µmol/L. A C_{max} of 10.8 µmol/L (3740 ng/mL) was reported in AstraZeneca study 250 and without demonstrating any drug related side effects. Of the simulations, 8.6% (87 out of 1012) had any simulated concentration above this value. Overall, there was a similar distribution of C_{max} between groups, however in the dosage groups >1 year and weighting between 5<10 kg, and <1 year, weighting above 10 kg, 16.7% and 12.5% respectively the highest simulated concentration above this value.

Figure 5 Simulated omeprazole exposure in children. (– · –) "20mg" and "40mg" represent the adult AUCs following dosing of 20 and 40 mg of omeprazole, respectively. (- -) "Maximum observed AUC in iv study" refers to the highest observed AUC 38.97 µmol.hr/L. The grey shaded boxplots refers the age group >1 year and dosing according to the current pediatric US PRILOSEC label. The white boxplots refers to the <1 year age group and the proposed dosing algorithm. (o) Represent AUCs derived from the estimated individual typical values of CL/F from studies 245, 250 and I-678. (o) Represent the AUCs derived from the reported CL following iv infusion of omeprazole. Boxes represent the first to third quartile and the bars extend to the last observation within 1.5 of the inter-quartile rage.



(Source: Applicant's Response to PMR Document, Figure 5)

Figure 6 Simulated maximum concentrations based on the proposed dosing algorithm for children <1 year, and according to the current US label for PRILOSEC in children >1 year of age. (--) represent the highest reported C_{max} from AstraZeneca study 250 of 10.8 µmol/L.



(Source: Applicant's Response to PMR Document, Figure 6)

Reviewer's Comments:

It is important to note these simulations include the PK variability defined from the entire pediatric population and that the simulations are not only for the fixed effect for each individuals varying demographics.

The applicant's exposure matching approach appears reasonable. It is unclear where the additional numbers of subjects in their figures 5 and 6 come from. There were 253 in their simulation dataset (Table 3) whereas figures 5 and 6 suggest there are 1012 subjects in the simulation. The reviewer's analysis repeated this simulation with the

applicant's simulation dataset that was comprised of 253 subjects. The results are consistent with the applicants and are shown in Figure 1.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The applicant's population PK model and simulation datasets were reviewed to ascertain the relevance of the covariates and the expected exposures for the relevant safety database.

4.2 Objectives

Analysis objectives are:

1. Simulate predicted exposures for the dosing regimen of 1.5 mg/kg that was evaluated in study 251 with the applicant's simulation dataset.
2. Simulate the effect of age on clearance to better understand if the relationship developed from literature is consistent with expectations for the effect of age on clearance.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
PopPK Report	Pedd1ka1.csv	\\cdsesub1\evsprod\nda022056\0118\m5\datasets\pooled-datasets\analysis\legacy\datasets\
PopPK Report	Simdata30.csv	\\cdsesub1\evsprod\nda022056\0118\m5\datasets\pooled-datasets\analysis\legacy\datasets\

4.3.2 Software

The statistical software R (version 2.15) was used for all plots and figures. NONMEM (Version 7.3) was used for rerunning the applicant's population PK models.

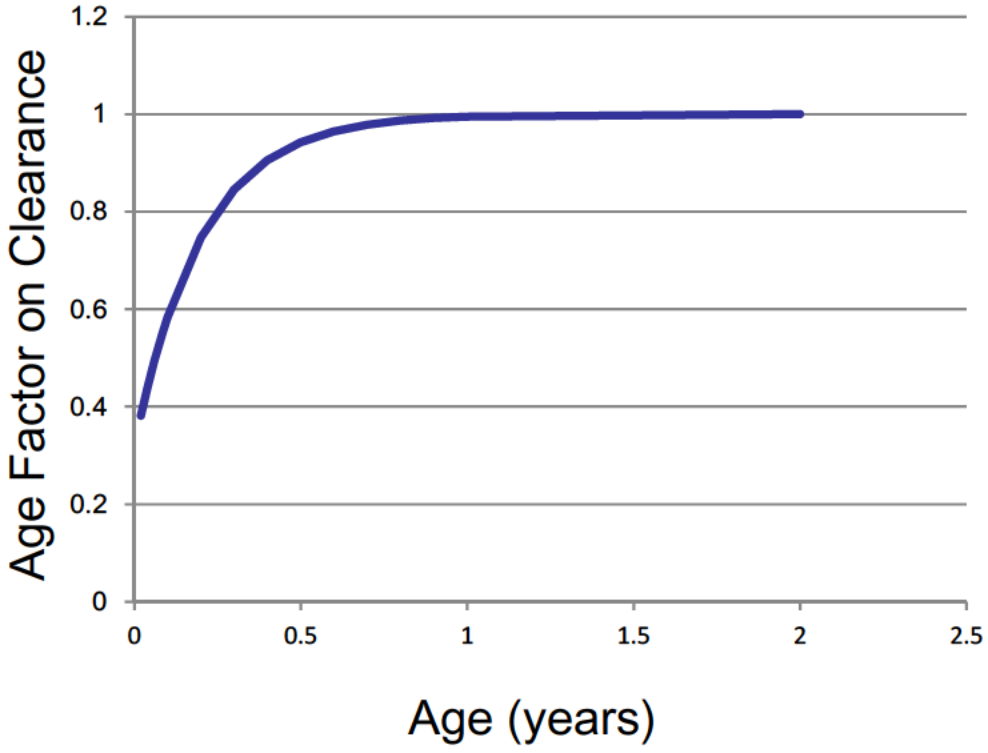
4.3.3 Models

No original modeling was performed by the FDA.

4.4 Results

Figure 5 shows the effect of age on clearance based on the applicant's population PK model. It is consistent with expectations that age effects attributed to maturation of enzyme expression should by matured by 1 or 2 years.

Figure 5. Modeled effect of age on clearance.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
SimPK_Std250.R	Review Graphs	\PM Review Archive\2016\Prilosec (Omeprazole)_NDA22056_JCE\PPK_Analyses
Run* mod	NONMEM Run Files	\PM Review Archive\2016\Prilosec (Omeprazole)_NDA22056_JCE\PPK_Analyses\NONMEM_prilosec\

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