Model-dependent pharmacokinetic analysis of enalapril following the administration of novel child-appropriate orodispersible mini-tablets

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i. Erklärung

Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der “Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die Dissertation wurde in der vorgelegten oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den Muhammad Faisal

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III. Summary

Despite the legislative initiatives by the regulatory European medical agency (EMA) and the United States Food and Drug Administration Authority (FDA), an approved drug with child-appropriate dosage formulations are still absent for many drugs for pediatric heart failure. The pediatric patients are usually treated by extrapolating adult treatments to children without considering the important physiological, biochemical and pathological differences. The lack of approved child-appropriate dosage formulation leads to inaccurate off-labeled extemporaneous administration of drugs. Off-labeled use of drug and dosage form has put the pediatric population at severe risk of adverse drug reactions or no therapeutic action and warrant the need to develop a safe and effective child-appropriate dosage formulation for the treatment of pediatric heart failure. The child-appropriate orodispersible mini-tablet formulation of enalapril was developed and tested during the LENA (labeling of enalapril from neonates till adolescents) clinical trials initiated and funded by the European Union project under the 7th framework program. A 3-period 3-treatment crossover phase I clinical trial was conducted in the project in which the developed novel child-appropriate orodispersible mini-tablets and reference formulation were administered to 24 healthy adult volunteers. Full profile serum samples were analyzed using an individual pharmacokinetic modeling analysis and least square minimization method of parameter estimation to account any difference in the pharmacokinetics of enalapril when was administered from the dispersed and administered orodispersible mini-tablets and reference formulation. For the comparison of the biotransformation and pharmacokinetics of active enalaprilat from the two formulations, a combined serum and urine enalapril and enalaprilat models were developed and the maximum likelihood method of parameter estimation was used for parameter estimation.

The estimated individual pharmacokinetic parameters were compared to account for any difference in the pharmacokinetics of the two formulations. In addition, the covariate effect of the formulation was evaluated on the model parameters. The pharmacokinetic modeling analysis revealed 5 minutes of an early appearance of enalapril from the developed child-appropriate orodispersible mini-tablets

administered with 240ml water compared to the reference formulation. No other difference in the pharmacokinetics of enalapril and enalaprilat was observed from the two formulations. The modeling analysis also showed that enalapril had similar bioavailability and pharmacokinetics from the orodispersible mini-tablets and the reference formulations and thus is highly suitable to be safely and effectively use in children.

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VII. List of Abbreviations

ACE-I	Angiotensin-Converting Enzyme Inhibitor
CES-I	Carboxylesterases Enzyme Inhibitors
CV	Coefficient of Variation
CI	Confidence Interval
CWRES	Conditional Weighted Residuals
CHF	Congestive Heart Failure
EU	European Union
EMA	European Medicine Agency
FDA	Food and Drug Administration Authority
FOCE+I	First Order Conditional Estimation with Interaction
F1	Bioavailability
ICH	International Conference of Harmonization
IRLS	Iteratively Reweighted Least Square
KA	Rate Constant of Drug Absorption
KE	Rate Constant of Drug Elimination
KREN	Rate Constant of Renal Drug Excretion
KM	Rate Constant of Metabolite Formation
KME	Rate Constant of Metabolite Elimination
KQ1	Rate Constant of Inter-compartmental Distribution
KQ2	Rate Constant of Inter-compartmental Distribution
LSMM	Least Square Minimization Method
MTT1	Mean Transit Time of Drug Absorption
MTT2	Mean Transit Time of Metabolite Formation
ODT	Orodispersible Tablets
OLS	Ordinary Least Square Minimization Method

ODMT	Orodispersible mini-tablets
PRED	Population Predicted Concentrations
RSE	Relative Standard Error
SD	Standard Deviation
SSR	Sum of Squared Residuals
SIR	Sampling Importance Resampling
Tlag	Lag Time of Drug Absorption
VM	Volume of Distribution of Metabolite
VC	Volume of Distribution of Parent Drug
VPC	Visual Predicted Check Plots
WRES	Weighted Residuals
WHO	World Health Organization

Chapter 1

Introduction and background of the development of child-appropriate dosage formulations for the treatment of heart failure in pediatrics.

1.1. Background

Children have been treated as therapeutic orphans. Compared to adults, only a score of drugs and dosage formulations are tested for efficacy and safety determination in the pediatric population and are mainly used off-labeled.[1] Even most of the licensed products for adult administration lack appropriate palatable, stable and safe dosage formulations to deliver low doses of drugs required for pediatric treatment. This leaves the pediatric health practitioners with no choice other than to prescribe off-labeled drugs and dosage formulations, which can compromise the safety and efficacy of the drug products.[2] Similarly, due to lack of sufficient data to examine the pharmacokinetics, efficacy, and safety of a drug product and dosage formulations, approved drugs and dosage formulations for many drugs are absent for the treatment of Congestive Heart Failure (CHF) in the pediatric population.[3] The off-labeled use of drugs may lead to sub-therapeutic levels in pediatrics to treat heart failure, may show no therapeutic effect and can lead to severe disease progression.

1.2. Regulatory prospects

The regulatory authorities and health practitioners have recognized the serious risks and consequences of the use of off labeled drug and dosage formulation in pediatric administration, which include the compromised safety and efficacy, administration difficulties and failures, and non-adherence to therapy.[4] The number of approved drug products with information for pediatric administration has improved in the last decades depicting the fruitfulness of regulatory efforts in the labeling of drug products for pediatric administration.[5] This is attributed to the legislative and incentive initiatives driven by regulatory authorities like the United States of America Food and

Drug Administration Authority (FDA) and the European Medicines Agency (EMA) to persuade pharmaceutical companies to include additional pediatric investigation studies in their drug development programs.[6] As a reward, the FDA Modernization Act of 1997 section 111[7] and Best Pharmaceuticals for Children Act 2002[8] offered an additional 6 months of market exclusivity to the companies that investigate medicinal products in pediatric patients.

In 1997, a round table discussion of pediatric experts was organized by the European Commission to discuss pediatric medicine and supported the need to internationally discuss the performance of pediatric clinical trials in the context of the international conference of harmonization (ICH). The ICH guidelines (ICH Topic E11) entitled "*Clinical investigation of medicinal products in the pediatric population*"[9] supported by the European Commission were agreed and has been enforced since 2002.[10] In 2003, pediatric investigational studies became mandatory for products to be used in children under the United States Pediatric Research Equity Act.[11] Furthermore, the prescription Drug User Fee, FDA Amendments ACT of 2007, and European regulations updated the clinical trial requirements and the incentives as a reward for conducting pediatric drug development.[12] Similar to the USA FDA Modernization Act of 1997, the European Union's (EU) new regulation on medicinal products for pediatrics was enacted and has improved the availability of pediatric medicine in the EU.[13] These legislations have made it necessary for the companies to conduct pediatric clinical trial programs on medicinal products to account the safety and efficacy of drug and dosage forms for the administration in pediatrics patients.[14]

1.3. Lack of child-appropriate dosage forms for pediatric heart failure

According to the EMA, age-appropriate dosage formulation is the one that is appropriate for use in all target age groups, acceptable by the pediatrics and able to be used and administer by the caregiver.[15] These formulations should contain safe stable and well-established excipients.[13] Different dosage formulations are considered appropriate for pediatrics administration.[16] However, no formulation has yet been approved to be a child-appropriate formulation in the treatment of heart failure and are

used off-labeled. Off-label use is the intentional use of approved products against the terms and conditions of market approval and is not in agreement with the summary product characterization (SmPC).[17]

In the year 2000, the European Network on Drug Investigation showed that around 50 percent of pediatric drugs are being used off labeled in hospitals.[13] Thirty-two studies for the investigation of off-label use of drugs in pediatrics in the hospital setup showed around 13-69% of drug prescriptions were being off-labeled. This range was wider i.e. 2-100% off-label prescriptions in outpatient settings.[17]

Table 1-1 Example of authorized oral dosage formulation for use in pediatrics.

Dosage forms	Age	Drug	Comment	Company
Solid Capsule	≥ 6 years	Methylphenidate	SODAS® (Spheroidal Oral Drug Absorption System) technology	Ritalin LA® (Novartis)
Orodispersible films	≥ 0.5 years	Ondansetron		Setofilm® (APR and Labtec and Monosol Rx)
	≥ 2 years	Sennosides		Pedia Lax® (Fleet)
	≥ 4 years	Diphenhydramine/ Phenylephrine		Triaminic® Thin Strips™ cold and cough (Novartis)
ODT/melting tablet	>2 years	Ondansetron		Ondansetron ratiopharm® ODT
	>1 year	Lansoprazole	Delayed-release ODT (e.g., suspended in an oral syringe)	Prevacid® (Takeda)
	≥6 years Ibuprofen	Ibuprofen		Nurofen® (Reckitt Benckiser)
Tablet	≥6 years	Ibuprofen		IBU-ratiopharm® (Ratiopharm)
Liquids Suspension/ solutions	> birth	Antibiotics, e.g., amoxicillin	Constitution to a suspension. The mixture to be dissolved in water	Oralpädon® (Stada)
Microcapsules/ -spheres	>1 year	Ciprofloxacin	Constitution to a suspension	Cipro® Bayer

Due to the lack of age-appropriate dosage formulations, the solid dosage forms, like tablets and capsules manufactured for adult administration, are manipulated by

crushing or opening the contents for use in pediatrics. This off labeled use of extemporaneous preparations can potentially result in compounding errors and dosing inaccuracies. Pharmacokinetic/pharmacodynamics or bioavailability studies for these extemporaneous preparations are rarely conducted due to financial constraints and technical complexity of conducting these studies. In addition, the use of these preparations are based on personal experiences and are hardly tested for stability, sterility, and are not evaluated in randomized control trials for the determination of efficacy and safety.[18] This suboptimal practice of pediatric administration has put the pediatric population at possible risks of severe adverse effects and may result in no therapeutical benefit due to the low concentration level of drugs in serum that may treat the diseases.[19]

The selection of dosage formulation for pediatric administration possesses certain challenges. The pediatric population represents a heterogeneous age group; therefore, the child-appropriate dosage formulation must contain special properties. Child-appropriate dosage formulations should provide dose precision, safety, no swallowability issues, microbial, chemical, and physical stability, ease of transport, should be palatable, taste masking, dose flexible, should ensure content uniformity, appearance, and low cost.[20] Therefore, there is a need to develop and approve safe and effective child-appropriate dosage formulations of the drugs especially for the treatment of chronic illness like pediatric heart failure.

1.4. Commonly used dosage formulations for pediatric administration

Different novel and conventional dosage formulations that are administered through different routes and are considered for off-label administration in the treatment of pediatric heart failure. Off-label use of these formulations offers certain advantages and disadvantages for pediatric administration. Some of these formulations are discussed below with their advantages and certain disadvantages;

1.4.1. Oral dosage formulations for pediatric administration

Around 70 percent of the pediatric investigation plan for cardiovascular diseases used oral formulations and around 70 percent of the total number were solid oral dosage forms.[21] Oral dosage forms are the preferred form of drug delivery due to certain advantages including the ease of administration, the ability for self-medication with accurate dosing without any pain and improved patient compliance and high medication adherence. Despite that, these dosage forms possess some challenges in administration to special populations like pediatrics, geriatrics or mentally retarded patients.[22]

1.4.1.1. Oral liquid formulations for pediatric administration

Drugs can be administered in the form of liquid formulations such as syrups, solutions, dispersions, emulsions, suspensions, elixirs, tinctures, liniments, sprays, and aromatic water, etc.[6] EMA recommends the use of oral liquids when they are administered with an appropriate volume of vehicle. According to the EMA draft guidelines, the appropriate volume of the liquid vehicle is 5ml for less than 4 years old patients and 10 ml for pediatric patients of age 4-12 years.[116] Previously, EMA had recommended in the reflection paper "*Reflection Paper: formulations of choice for the pediatric population''*, the liquid formulations to be appropriate and formulation of choice for pediatrics administration in less than 8 years of age.[24] These formulations are considered suitable for full-term birth and preterm neonates who can swallow enteral feedings.[25]

Oral liquid dosage formulations were considered the most favorable for pediatric administration as they offered increased dose flexibility compared to all other formulations and could be tailored for a wide age range. Oral liquids provide taste masking of bitter drugs and improve palatability, which is reported to be the greatest barrier in providing pediatric treatments.[26]

These dosage forms offer some limitations, including the lack of controlled-release formulations for multiple-dose administration, difficulty in transport and its higher cost due to larger bulk size, lesser shelf life compared to solid formulations and special

storage requirements. In addition, special techniques or additional excipients are required to overcome the problems like formulation of low solubility drugs, chemical instability of active part, the susceptibility of degradation and microbial growth, which can alter the pH, odor, smell, appearance and hence palatability, and selection of safe preservatives according to the target age group.[25,27]

1.4.1.2. Solid conventional dosage formulations for pediatrics

In the year 2008, the expert forum of the World Health Organization (WHO) proposed solid oral dosage forms for pediatric administration.[13] Solid conventional tablets or capsules may be manipulated for pediatric administration. These solids unit tablets are sometimes crushed or the capsules are emptied for reconstitution with water to form a suspension prior to their administration.

Solid conventional dosage forms offer to prolong stability, ease of transportation, and low cost of manufacturing, therefore they are considered as the formulation of choice in the pharmaceutical industry. Solid dosage formulations can be a film or sugarcoated to mask the taste, they provide better adherence and ease of administration.[6]

These dosage formulations are usually considered acceptable as a whole in pediatrics above 6 years of age, who may also find some difficulties in swallowing.[24] Pediatrics at an early age are not able to swallow the conventional tablets and the extemporaneous preparation of these dosage formulations is dispensed for administration. Scoring or break line is usually given on these tablets to split it for dose and size adjustment.[4] Sometimes tablets are crushed and the powder is then administered as suspension. Drugs dispensed as coated tablets cannot be dispensed extemporaneously due to its effect on bioavailability and the loss of coating if these tablets are crushed or broken. The extemporaneous preparations may compromise the uniformity of dosage forms and can lead to failure of the drug to reach a minimum therapeutic concentration in the blood. The solid dosage formulations are less dose flexible compared to oral formulations.

Capsules of size 11.1 mm to 23.3 mm may be used in intact form or the contents are emptied and administered to the patients. Data related to the acceptability of capsules is limited. The bitter taste and poor bioavailability may affect the adherence, efficacy, and safety of drug products.[23] Special care should be exercised in pediatric administration to avoid possible risks associated with choking, chewing or aspiration or acceptability of different capsule sizes.[28]

1.4.1.3. Other orally administered tablets for pediatric administration

a. Orodispersible tablets for pediatric administration

Oral dosage forms have evolved from the conventional solid tablets to the modified-release formulation and are now adding the novel Oro-Dispersible Tablets (ODT) in their class, which disintegrates quickly in the mouth when exposed to saliva and solves the problem of dysphagia.[29] These dosage forms provide advantages of stability, dose flexibility, high bioavailability, compliance, and adherence[30] However, these formulations need sophisticated technology and equipment, which may increase the cost of manufacturing, as they need. These formulations need specialized packaging to avoid physical degradation due to moisture sensitivity. Palatability, fast disintegration, hygroscope, and mechanical strength are the challenges associated with the development of ODT.[6]

b. Wafers, orodispersible films, and lyophilisates, for pediatric administration

Fast disintegrating wafers are placed on the tongue and it sticks to the oral mucosa to release the drug when it is exposed to water through fast-dissolving polymers. These wafers are of 2-8 cm^2 area size and have a thickness of 20-500 um. These dosage forms have advantages, which are needed to be present in a child-appropriate dosage formulation like dose accuracy, less choking risk, portability, improved bioavailability. However, these formulations cannot be used for high dose administration and possess problems of content uniformity.[6,31] The orodispersible films consist of single or multilayers sheets which are rapidly dispersed on oral administration. These films have a size of 2 x 4cm and are packed in sealed moisture resistant packages.

A pediatric investigational plan was agreed by the EMA for orodispersible film formulation developed by Pharmathen for the treatment of pediatric hypertension in children of age greater than 1 year. Similarly, a formulation of ondansetron has been licensed for children over 6 months of age. However, at present no orodispersible tablets are licensed for pediatric administration and no data has been published related to the acceptability of these formulations in pediatrics.[32, 33] Orodispersible lyophilisates are prepared from the suspension or solution of active pharmaceutical agent freeze-dried in the blisters. They offer high patient satisfaction, however, they are expensive and are not feasible to use for by the visually impaired patients.[32]

c. Dispersible tablets for pediatric administration

Dispersible tablets have been used for the treatment of antiretroviral therapy in pediatrics and zinc treatment for childhood diarrhea. These formulations are dispersed in water within 3 minutes into a uniform dispersion before administration. These formulations need a larger volume of water and are therefore not recommended for a lower age range.

d. Effervescent tablets for pediatric administration

These tablets are also dispersed in a large amount of water for administration. These tablets may enhance the absorption of drugs by the bubbling effect of carbon dioxide in the intestinal epithelium. These formulations require a large volume of water and are therefore not suitable for early age children.[28]

e. Chewable tablets for pediatric administration

These dosage forms are administered in children of more than 2 years of age. These dosage forms are safe, palatable, well-tolerated, and do not require water for administration. They are intended to be chewed and are not swallowed therefore they are recommended in children greater than 6 years of age. These formulations present disadvantages like choking, overdosing, dose flexibility, palatability, and the safety of excipients.[34]

f. Powders or granules for pediatric administration

These dosage forms are dispersed in water for oral administration. In these formulations, sweeteners, stabilizing agents, suspending agents, colorants are used as excipients. Powders present advantages of easy swallowing and dose flexibility however they may present palatability problems.[34,6]

g. Buccal and sublingual tablets for pediatric administration

These preparations are not recommended for administration in children because of their longer contact time with saliva.

1.4.2. Parenteral dosage formulations for pediatric administration

Parenteral preparations are administered through intravenous bolus, subcutaneous, and intramuscular routes. These preparations are usually reserved for critically ill pediatric patients to get prompt action.

Parenteral preparations need specialized training, facilities, and qualified personals right from the manufacturing process to their administration. These preparations can cause physiochemical problems, volume overload problems, compatibilities with other active ingredients, osmolality problems, overdosing or under-dosing, compliance problem and pain.[6]

1.4.3. Nasal Preparations for pediatric administration

Nasal preparations can be used to deliver the drug in all age ranges. Careful considerations should be made regarding the acceptability, irritation, sensation, pain, of the active agent on the administration of nasal preparations.[6]

The advantages and disadvantages of all the above mentioned dosage formulations have been summarized in **Table 1-2**. The disadvantages of these formulations make them unsuitable especially for chronic administration, and neonates in treating pediatric heart failure. Ideal child-appropriate dosage formulations are still missing and there is a need to develop and approve safe, effective, dose flexible, stable, acceptable and

palatable dosage formulations for the administration in pediatric heart failure patients, which should also be evaluated for their safety and efficacy in terms of bioavailability and bioequivalence studies for pediatric administration.

Table 1-2 Advantages and disadvantages of different formulation for use in pediatrics

Administration and Dosage Forms	**Major Advantages**	**Major Disadvantages**
Oral Liquids	Dosing flexible	Stability issues, high cost.
Solid conventional tablets	Ease of administration	Swallowing, choking problems.
Parenteral	Prompt action	Painful, Compliance, adherence issues for chronic use.
Nasal preparation	Wide acceptability for the age range	Irritation, pain, and compliance.
Powders and granules	Ease of swallowing and dose flexibility	Palatability and chocking issues.
Effervescing and dispersible tablets	Prompt action	It can lead to volume overload, palatability issues.

1.5. Orodispersible mini-tablets: A novel dosage formulation for pediatric administration

Orodispersible mini-tablets usually have a size less than 4 mm. They are smoothly dispersed immediately after getting in contact with a small amount of saliva. This facilitates the administration of drugs in neonates and toddlers and makes the orodispersible mini-tablets to be suitable for pediatric administration even at younger ages. Small-sized (1-4mm) tablets are now considered acceptable by the regulators for young children of age between 2-5 years.[35] Whereas the orodispersible mini-tablets, which are intended to be dissolved in the mouth, have been considered for administration in children of greater than 1 month to 2 years of age. A randomized controlled trial study conducted by Klingemann et al concluded orodispersible mini-tablets to be superior for pediatric administration compared to the liquid formulations. Even the 25 mini-tablets administered to pediatrics above 6 months of age were

acceptable and safe. The ability to take at once the number of safe and acceptable orodispersible mini-tablets increases to 400 mini-tablets when administered to pediatrics of above 1 year of age.[36] These tablets have all the advantages of solid dosage formulations and in addition, contain the age-appropriate property of larger dose flexibility and physical and chemical stability. Due to dispersion in the mouth, these formulations reduce the risk of choking, particle sensation and aspiration. At present, no approved product with orodispersible mini-tablets is available for commercial use. The 1 and 2 mm sized orodispersible mini-tablets have been manufactured and met the requirements of content uniformity set by the European pharmacopoeia[37] Stoltenberg *et al,*[38] manufactured the small 2 mm sized orodispersible mini-tablets of enalapril by compressing the powdered blend containing ready-to-use excipients like Ludiflash (BASF, Ludwigshafen, Germany), Pearlitol Flash (Roquette, Lestrem, France), Parteck ODT (Merck, Darmstadt, Germany), Pharmaburst 500 (SPI Pharma, New Castle, USA) and Prosolv ODT (JRS Pharma Rosenberg, Germany).[38] Martin Homes developed the first orodispersible mini-tablet formulation with enalapril. The formulation is yet not approved for the administration in pediatric heart failure and is under investigation within the LENA clinical trials.[21]

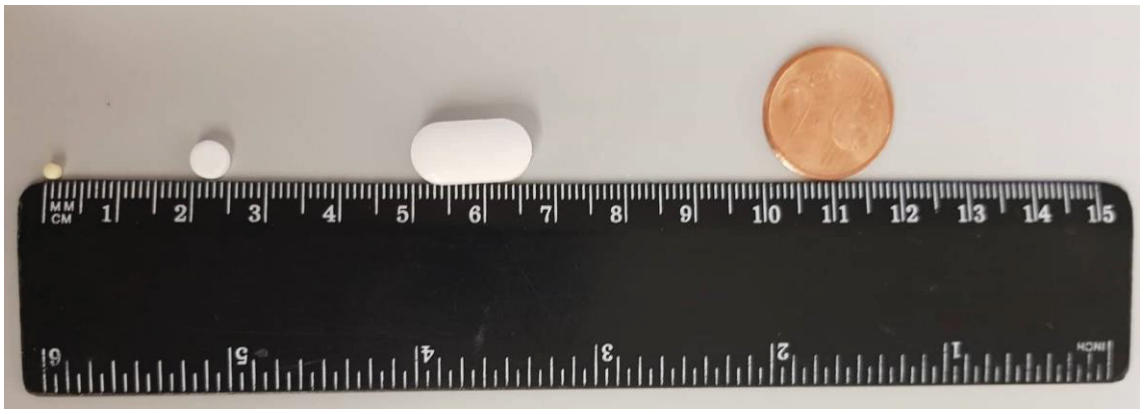


Figure 1-1 Size comparison of orodispersible mini-tablets with commonly used products. From left to right; ODMTs, Sucral tablets, Paracetamol 500mg tablet, 2 cent coin.

As per European medicine agency guidelines "*Note for the guidance on the investigation of bioavailability and bioequivalence*", the application for new products containing already approved active substances requires in vivo bioequivalence studies.[39] Because

of the difficulties in conducting clinical trials, the new child-appropriate dosage formulation cannot be tested for bioequivalence in the sensitive pediatric population. Therefore, the European medicine agency suggests to conduct the clinical trials in adults and to extrapolate the information to pediatrics.[40] As a step towards the provision of a novel child-appropriate oral dosage formulation for drugs and of enalapril for the treatment of heart failure in the pediatric population, these orodispersible mini-tablets have been evaluated for the bioequivalence and bioavailability using non-compartmental analysis, and palatability evaluation during the LENA clinical trials.[41] Further pharmacokinetic evaluation is being carried out to access the safety and efficacy of these dosage formulations prior to the administration in pediatrics heart failure patients.

1.6. Pathology and treatment of cardiac heart failure

Cardiac heart failure is a pathological and clinical syndrome in which the heart fails to pump an adequate amount of blood in order to meet the metabolic needs of body tissues.[42] In adults, the syndrome is characterized by signs and symptoms related to edema, exercise intolerance, respiratory distress, growth failures, and neuro-hormonal disturbances,[43] while heart failure in pediatrics is caused due to the volume overload or afterload with or without pathological myocardium.[42]

Around 10-33% of all the cardiac pediatric patients are related to heart failure. Different classes of drugs are used for the treatment of heart failure in pediatrics with the aim to improve cardiac output, decrease volume overload and afterload conditions and to treat the remodeled heart. Diuretics, beta-blocking agents, angiotensin II receptor blockers, inotropic agents, vasodilators, sympathomimetic amines, calcium sensitizer and phosphodiesterase type III inhibitors have been tested to use in the treatment of pediatric heart failure.[42] The Pediatric Heart Failure Expert Group meeting held by the European Medicine Agency has recommended angiotensin-converting enzyme (ACE) inhibitors as the first-line treatment for chronic heart failure in pediatrics with emphasis to evaluate safety-related data for the chronic use of these medicines.[44] Enalapril inhibits the renin-angiotensin-aldosterone system and has proven to prolong survival in

heterogeneous small scale studies [45] and has been put onto the priority list of drugs to be developed for pediatric heart failure treatment. At present, the drug has not been approved for pediatrics under the age of 6 years or 20 kg in Europe.[46] The drug is an angiotensin-converting enzyme inhibitor and can cause the inhibition of chronic hyper-activated renin-angiotensin-aldosterone system, which is one of the major causes of heart failure.

- **Activation of the renin-angiotensin-aldosterone system**

Vasoconstriction, due to the thickening of tunica media muscles of the vessels during vascular remodeling and the hyper-activated sympathetic nervous system, can decrease blood flow to the afferent arterioles, which supplies the blood to the nephrons in the kidney. This fall of arterial blood pressure results in the stimulation of polkissen cells in the Juxtaglomerular apparatus. Renin is stored in the Juxtaglomerular apparatus in an inactive form called pro-renin which then split into renin upon stimulation of cells. The renin is then released into the efferent arterioles and further into the renal blood flow to enter the systemic circulation.

This circulating renin reacts to its substrate called angiotensinogen to form a 10 amino acid peptide called angiotensin I. Angiotensin I is a weak vasoconstrictor agent which splits in the vascular endothelium of lungs into an 8 amino acid peptide called angiotensin II by the enzymatic action of angiotensin-converting enzyme. Angiotensin II is a powerful vasoconstrictor agent, which binds rapidly to its receptors in the arterioles to causes vasoconstriction, which results in an increased total peripheral resistance and blood pressure. Angiotensin II also acts on its receptors in the venous capillary bed to cause constriction and reduced venous return.

Angiotensin II causes retention of water and salt by,

1. Direct action to constrict renal arterioles, which causes slow blood flow in peritubular capillaries and promotes fast absorption from tubules.

2. Angiotensin II powerfully stimulates adrenal glands to release aldosterone from zona glomerulosa into the systemic circulation to reach principle-cells. Aldosterone binds to the receptors in principle cells and causes modification of genes to produce Na+/K+-ATPase that are planted to the basolateral membranes of principal cells. These Na+/K+-ATPase transports sodium out of cell and influx potassium in the cells. In addition, sodium channels are produced by further genetic modifications in the luminal part of the membrane and start reabsorption of sodium into the cells and to the blood. Hence, more sodium and water are reabsorbed due to aldosterone, which overall results in an increase of systolic blood pressure and venous return.

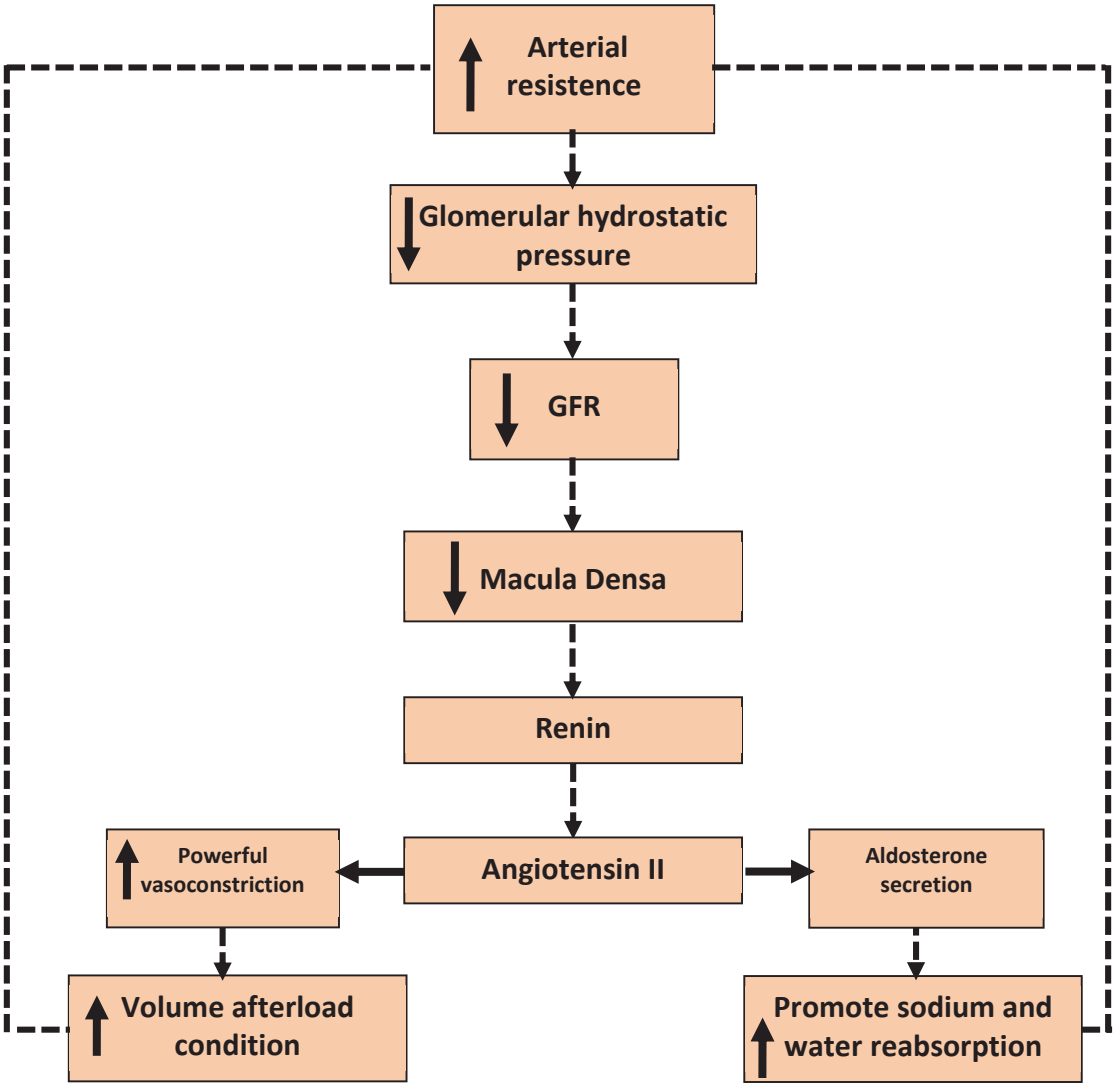


Figure 1-2 Schematic diagram of the renin-angiotensin-aldosterone system

3. Angiotensin II will act on the receptors of the hypothalamus and activate the supra-optic nucleus which stimulates the release of the anti-diuretic hormone from the posterior pituitary and increases the permeability of water from the last hypo-osmolar part of nephrons to hyper-osmolar interstitium, from where more water enters into the blood.

This overall activation of the renin-angiotensin-aldosterone system results in vasoconstriction and higher systemic blood volume, which causes high blood pressure in the arterioles.

- **Pathology of Heart failure**

One of the major causes of cardiac heart failure is the chronic hyper-activation of the renin-angiotensin-aldosterone system will cause the heart to pump under overloaded and after loaded conditions. This results in hyperactivity of heart muscles to improve the functionality of the heart and eventually results in pathological hypertrophy of heart muscle terms as heart remodeling. These results in a reduced ability of the ventricles to properly fill contract and eject an adequate proportion of blood into the systemic circulation (reduced ejection fraction, stroke volume and cardiac output) according to the metabolic needs of the body and is called heart failure.[47]

- **Clinical pharmacology of enalapril**

After Captopril, enalapril for oral administration was made commercially available for the treatment of hypertension.[21] Enalapril is an inactive prodrug that is bio-transformed in the liver by the Carboxylesterases-I (CES-I) enzyme into an active form called enalaprilat.[48] The metabolite inhibits the hyper-active renin-angiotensin-aldosterone system by inhibiting the angiotensin-converting enzyme, which is responsible for the conversion of angiotensin-I to angiotensin-II. This blocks the whole cascade of events associated with the formation of angiotensin II including direct arteriolar vasoconstriction and activation of aldosterone secretion. This will reduce volume afterload and overload condition and over the chronic use, it causes inhibition of heart remodeling.

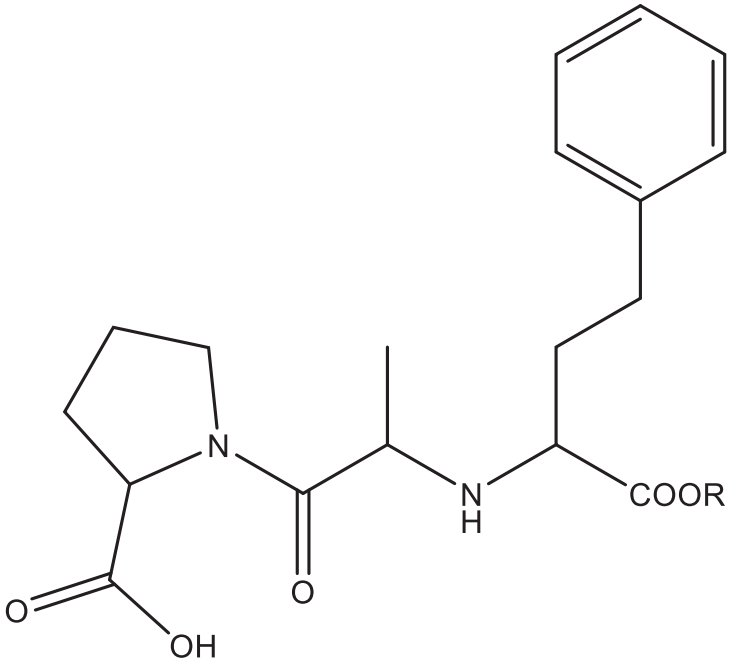


Figure 1-3 Chemical structure of enalapril (R= C_2H_2) and enalaprilat (R=H). IUPAC name: (2S)-1-((2S)-2-(((2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl)amino)propanoyl)pyrrolidine-2-carboxylic acid.

In adults, enalapril is proven effective in increasing cardiac output, stroke volume, exercise tolerance, ejection fraction, and NYHA classification. Enalapril is also effective in decreasing the pulmonary capillary wedge pressure, mean arterial pressure.[49] Enalapril is usually administered in the initial dose of 5 mg and can be up-titrated to 10 mg, 20 mg or 40 mg once or twice daily depending on the intended pharmacological response.[50] Around 60 % of the administered oral dose of the drug is absorbed through the gastrointestinal tract into the plasma and achieves maximum serum concentration in 1 hour. The drug remains in the plasma for about 10 to 12 hours and is eliminated through the renal or metabolic route. Enalaprilat achieves its maximum plasma concentrations in around 3-4 hours. Enalaprilat concentrations can be detected in the body for around 72 to 96 hours and it is eliminated through the renal route without further metabolism.[49] Around 60 % of the total amount of administered dose is recovered in urine as enalapril and enalaprilat.[48] At present, no other route of elimination has been reported for enalapril and enalaprilat.

At present, large scale, randomized placebo-controlled clinical trials have not been conducted in the pediatric population to generate enough data relating to the efficacy

and safety of enalapril in pediatrics. Only a few randomized clinical trials have been conducted but there are limitations reported in these studies.[51] Small scale testing of enalapril has been performed in which enalapril is proven effective to reduce afterload pressure, blood pressure, left atrium size, left ventricular end-diastolic blood pressure, liver size, respiratory rate. The drug also improves systolic performance, left ventricular loading conditions, heart rate, cardiac output, and renal function. Some studies reported no effect of enalapril. However, a number of studies have been reported to have positive effects of enalapril. [27,43,50,52–55,55,56,56–59] At present, enalapril is commercially available in a dose strength of 2.5, 5, 10 and 20 and 40 mg commercial tablets. Due to the absence of child-appropriate formulation of enalapril, these tablet formulations are used off-labeled for administration in pediatric heart failure patients.

1.7. Mathematical models for the comparison of pharmacokinetics of dosage fomulations.

Within the LENA project, the first mini-tablet with enalapril was developed by Martin Hermes. Two different dose strengths of 0.25 mg and 1 mg. LENA project, a child-appropriate orodispersible mini-tablet has been developed for the administration in pediatric heart failure patients and bioequivalence studies have been conducted in the adult population to compare the pharmacokinetics of enalapril and enalaprilat administered from reference and developed child-appropriate orodispersible mini-tablets. However, the non-compartmental analysis only provides limited information related to the total exposure of the drug in serum i.e. area under the curve (AUC), the maximum concentration of drug achieved in serum (Cmax) and the time a drug takes to achieve maximum concentration in serum (tmax).

Mathematical pharmacokinetic models are used to get complete and deeper insights related to the absorption and disposition of a drug in the body. The parameters of these models give in-depth information on the transfer of drugs from one compartment to another compartment. Rate constants and delay of absorption and formation of drug and their metabolite provides deeper insights, which can be used to infer and compare the onset of action through different dosage forms. The elimination rate constants and

volume of distribution can be used to determine and compare the physiological state of the subjects and the disposition of the drug in the body. The models can be further used for the prediction of the pharmacokinetics of drugs and metabolites at different doses and frequencies. The models can also be used to extrapolate the pharmacokinetics of drug and metabolite from adults to pediatrics using the allometric scaling.

In addition, the detailed pharmacokinetic evaluation of enalapril and enalaprilat in adults utilizing the full profile rich data set shall give prior knowledge regarding the pharmacokinetics of the drug and the metabolite and can be used in pediatric model development to predict the sparse concentrations.

1.8. Summary and Aims of the thesis

Treatment and management of pediatric heart failure have usually been based on evidence of heart failure treatment in adults due to a lack of pediatric clinical trials and subsequently a lack of approved drugs for children.[60,43] Despite major successes of the legislative initiative by the regulatory authorities, no drug has been successfully approved under these legislations for the children of the United States of America and European children suffering from heart failure. This is regarded as a severe risk for children because pediatric heart failure is characterized by high mortality rates.[61] Since the developing child undergoes maturation, growth[62,63] and shows different etiology of heart failure compared to adults,[64] pharmacokinetics and pharmacodynamics are different and therefore dosing regimens for children are also considered to be different.

Angiotensin-converting enzyme inhibitors have been recommended as the first-line treatment for chronic heart failure in pediatrics with emphasis to evaluate safety-related data of the chronic use of these medicines.[44] The Angiotensin-converting enzyme inhibitors enalapril has proven to prolong survival[45] and has been put onto the priority list of drugs to be developed for pediatric heart failure treatment.[65] At present, the drug has not been approved for pediatrics under the age of 6 years or 20 kg in Europe.[46]

Drug formulations, like liquids and suspensions, are usually recommended for children but excipients and the specific challenges of palatability limit their use. Solid dosage

formulations have advantages in this regard because they do not need excipients and can be masked for bitter taste. For children, solid dosage forms usually have to be crushed and used as extemporaneous preparations resulting in compounding errors and dosing inaccuracies.[27,66] To account for these problems, child-appropriate, solid dosage forms like orodispersible mini-tablets are considered as a preferred choice of a dosage formulation for drug administration in children.[26] Moreover, they offer reduced transportation costs to developing areas [38] than larger solid formulations.[67]

World Health Organization,[68] and European Medicine Agency have emphasized the need to develop child-appropriate dosage formulations[28] and the European Commission has launched an investigator-driven drug development programs for children[69] for innovative child-appropriate formulations covering highly needed pediatric indications such as pediatric heart failure treatment with enalapril. In the LENA project, the investigator-driven trials was planned to generate necessary data for devising a paediatric-use marketing authorization (PUMA). Within this program, enalapril, as orodispersible mini-tablet has been developed for children and a bioavailability study, had been conducted in healthy volunteers[35] comparing the orodispersible mini-tablet formulation with the market available generic formulation of enalapril (Renitec®).[35]

A detailed pediatric investigation is required to determine the efficacy and safety of enalapril in pediatrics for the treatment of heart failure. The regulatory authorities have focused on the development of better compliant, dose flexible, stable child-appropriate dosage formulations, which can maintain efficacy and safety of the drug and can deliver target drug concentrations in the blood for therapeutic effect.

Biopharmaceutical evaluation of child-appropriate formulation is difficult due to ethical and consent related constraints. As in adults, the vulnerable children population cannot be hired in clinical trials for biopharmaceutical evaluation without any intended medical benefit. Therefore, the developed child-appropriate orodispersible mini-tablet must be evaluated in adults for biopharmaceutical evaluation, pharmacokinetic comparison, safety assessment and compliance with the aim of extrapolating these results to the pediatric population.[70]

Typically, non-compartmental pharmacokinetic analysis is performed to compare the bioavailability of drugs reflected by the rate and extent (area under the curve and maximum serum concentrations) to which the active pharmaceutical ingredient or prodrug is absorbed from a drug product into the systemic circulation.[71] However, a pharmacokinetic modeling analysis can inform deeper insights into the pharmacokinetics of enalapril and enalaprilat.

• Aims and objectives

The overall aims of this thesis are given below. In addition, in chapter 2 and chapter 3 the respective sub aims and objectives are given.

1. Evaluate and compare the pharmacokinetics of enalapril administered using a dispersed and administered child-appropriate orodispersible mini-tablets with the already approved enalapril formulation using individual pharmacokinetic modeling approach and the classical least square minimization method of parameter estimation **(chapter 2, p. 21).**
2. To build a semi-mechanistic population pharmacokinetic model analysis using a non-linear mixed effect modeling approach for the detailed evaluation and comparison of the combined pharmacokinetics of enalapril and its active metabolite enalaprilat in serum and urine from child-appropriate orodispersible mini-tablets and the reference formulation **(chapter 3, p. 55).**

Chapter 2

Model-dependent classical pharmacokinetic analysis of enalapril administered to healthy adult volunteers using orodispersible mini-tablets

2.1. Introduction

Treatment and management of pediatric heart failure have usually been based on evidence of heart failure treatment in adults due to a lack of pediatric clinical trials and subsequently a lack of approved drugs for children.[60,43]

Due to various constraints in conducting pediatric clinical trials, new formulations are not tested for bioequivalence and bioavailability in pediatrics. Rather, the adult volunteers are hired and the biopharmaceutical results are extrapolated from adults to the pediatric population. Typically, non-compartmental pharmacokinetic analysis is performed to evaluate and compare the bioavailability of drugs reflected by the rate and extent (area under the curve and maximum serum concentrations) to which the active pharmaceutical ingredient or prodrug is absorbed from a drug product into the systemic circulation.[71] However, these parameters provide limited information related to the pharmacokinetics of drug and important parameters like rate constant of absorption (KA), rate constant of drug elimination (KE) clearance of drug, clearance of the metabolite, the volume of distribution (VD), and the onset of drug absorption (tlag) cannot be directly estimated. Mathematical models are used to estimate these parameters, which can explain the absorption and disposition of the drug in the body. These parameters can be estimated for each subject administered the different treatments and comparison of the pharmacokinetics can be made.

2.1.1. Classical pharmacokinetic modeling analysis

2.1.1.1. Mathematical pharmacokinetic models

Pharmacokinetic mathematical models can be useful in providing deeper insights related to the detailed pharmacokinetics of the drug administered from the developed test formulation versus the already marketed reference formulation. Especially the delay in onset of drug absorption can provide insights relating to the early or delayed onset of drug action through the child appropriate orodispersible mini-tablets compared to the reference tablet formulations. One, two or three-compartment models can be used to predict the pharmacokinetics of drugs depending upon the distribution of the drug in the central peripheral or deep tissue compartments.

Classical pharmacokinetic models can be used to estimate these pharmacokinetic parameters, which can predict the serum concentration data of the developed orodispersible mini-tablets and already marketed reference formulation. These parameters can be compared to evaluate any difference in the pharmacokinetics of the ODMT and the reference formulation.

Pharmacokinetic modeling analysis can be performed and model parameters can be estimated using a two-stage approach. In this method, the model is fitted to each pharmacokinetic profile to obtain the pharmacokinetic parameter information of that individual. The descriptive statistics are then applied to all the individual parameter estimates to calculate the population mean parameters.

2.1.1.2. Model parameter estimation using least square minimization method

Parameter estimation is a critical step in evaluating certain, reliable, unbiased parameters. Different methods of parameter estimation iterate different values of model parameters with variable accuracy and precision. A wrong parameter estimation can lead to a biased conclusion and correlation. Therefore, the selection of the appropriate method of parameter estimation should be given utmost importance.

One of the methods of model parameter estimation is the least square minimization method. The method estimates parameters that minimize the residual difference between the observed and predicted data.[72] Most commonly used least-square minimization methods are described below;

Ordinary least square minimization method (OLS), which minimizes the residual sum of square using a uniform weighting scheme, weighted least square minimization method (WLS) which uses reciprocal or reciprocal of the squared observed concentrations as weighting scheme and iteratively reweighted least square minimization method (IRLS) which uses reciprocal or squared of the reciprocal predicted concentrations in a reiterative manner as weighting scheme to estimate model parameters which minimize the residual sum of squares value.

As the above mentioned least-square minimization methods (LSMM) iterate different parameter values with variable accuracy and precision, therefore, the selection of the least-square minimization method of parameter estimation for modeling of enalapril data should be validated to select the LSMM which iterate the most accurate and precise model parameters. Then the parameters from the two formulations can be reliably correlated to account any difference in the pharmacokinetics of the two formulations.

Overall aim and objectives

The overall aim of Chapter 2 was to evaluate and compare the pharmacokinetics of enalapril administered using a dispersed and administered child-appropriate orodispersible mini-tablets with the already approved enalapril formulation using individual pharmacokinetic modeling approach and the classical least square minimization method of parameter estimation.

To achieve the main aim the analysis was subdivided into the following objectives,

- To conduct a **simulated validation step** for selecting the most accurate and precise least-square minimization method of parameter estimation for the individual pharmacokinetic modeling analysis.

- To perform **individual pharmacokinetic modeling** based on the simulated validation step to estimate parameters including lag-time of drug absorption, the rate constant of absorption the volume of distribution, and the rate constant of elimination of enalapril after the application of dispersed and administered 10 mg orodispersible mini-tablets and 10 mg of the reference generic formulation of the drug (5mg tablet) in healthy adult volunteers.
- To determine any difference in the pharmacokinetics of enalapril administered using the developed orodispersible mini-tablets versus the conventional reference formulation using **statistical tests.**
- To account for any **trans-mucosal** parallel absorption of enalapril from the dispersed orodispersible treatment of enalapril compared to the reference treatment arm.

2.2. Material and methods

2.2.1. The overall strategy of modeling analysis

In the first step, a simulated validation step was performed prior to the pharmacokinetic modeling analysis of the real data sets. The aim of the simulated validation study was to select an adequate least-square minimization method, which iterates the most accurate and precise parameters of the pharmacokinetic model. In the second step, the Individual time versus serum concentration profiles of each subject obtained after the administration of reference and developed formulations were subjected to pharmacokinetic modeling analysis and the pharmacokinetic model parameters were iterated using the most accurate and precise least-square minimization method of parameter estimation. The pharmacokinetic model parameters iterated for each treatment per subject were statistical compared to account any difference in the pharmacokinetics of enalapril administered from the two formulations.

2.2.1.1. Simulated validation step for the selection of accurate and precise least-square minimization method

2.2.1.1.1. Selection of pharmacokinetic model for the simulated validation step

The literature search and the goodness of fit plots indicated the one-compartment model to be adequate for the analysis of real data sets of enalapril concentrations,[73], therefore, a simulated validation process was carried out using the one-compartment model with the first order of absorption and elimination (Bateman function) **Equation 2-1**.

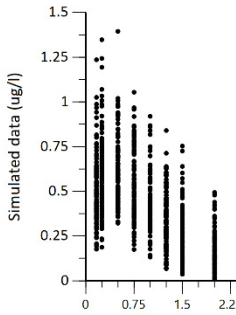
$$C(t) = \frac{\mathrm{dose}*\mathrm{f}}{\mathrm{VD}} * \frac{\mathrm{KA}}{\mathrm{KA}-\mathrm{KE}} * \left(e^{-\mathrm{KE}*t} - e^{-\mathrm{KA}*t}\right) \qquad \textbf{Equation 2-1}$$

*Where **dose** represents the administered amount of drug through extravascular route, **f** is the factor of bioavailability, **C** represents the concentration, **t** represents time point after drug administration, **KA** and **KE** represent rate constants of absorption and elimination and **VD** means the volume of distribution.*

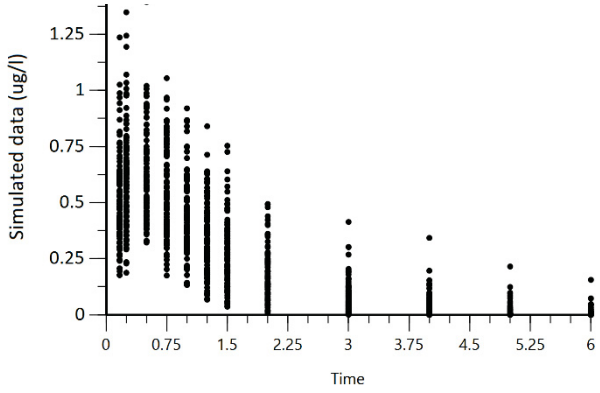
STEP 1: Generation of 100 fictive profiles using the parameters of the bateman function and random var

$$C(t) = \frac{dose * f}{VD} * \frac{KA}{KA - KE} * (e^{-KE*t} - e^{-KA*t})$$

Parameter	Geometric Mean	Geometric CV
KA (1/h)	5 1/h	30 %
KE (1/h)	1 1/h	30 %
VD (L)	100 L	30 %



STEP 2: Modeling analysis of the generated data for the selection of the most accurate and precise lea



$$C(t) = \frac{dose * f}{VD} * \frac{KA}{KA - KE} * (e^{-KE*t}$$

Least square minimization method (LS

Ordinary LSMM (Θ) = ∑ (Yi - f (pi, Θ))

Weighted LSMM (Θ) = ∑ (Yi - f (pi, Θ))

Iterative reweighted LSMM (Θ) = ∑ (Yi

Figure 2-1 Stepwise illustration of the validation step for the selection of accurate and precise least sq

2.2.1.1.2. Source data for the validation process

As a first step, an R program was written using R version 3.3 to generate simulated serum concentrations of 100 fictive subjects with predefined individual pharmacokinetic parameters. The predefined pharmacokinetic parameters were in line with the already reported values of enalapril in the literature.[73] To simulate the healthy population the values of each pharmacokinetic parameters of each subject were randomized with a lognormal distributed variability of 30 percent to imitate inter-individual variability given in **Table 2-1**;

Parameter	Geometric Mean	Geometric CV
KA (1/h)	5 1/h	30 %
KE (1/h)	1 1/h	30 %
VD (L)	100 L	30 %

Table 2-1 Geometric mean and coefficient of variation (CV) values of pharmacokinetic parameters of the Bateman function used for the generation of 100 fictive profiles.

Abbreviations: CV, coefficient of variation; KA, rate constant of absorption; KE, the rate constant of elimination; VD, apparent volume of distribution.

Based upon the generated random values of the set of pharmacokinetic parameters of all 100 subjects and the pharmacokinetic model **equation 2-1**, data sets of the concentration-time profiles at defined points of time were calculated by inserting individual set of pharmacokinetic parameters at each point of time **t** i.e at 0.167, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6 hour respectively. These time points were selected based on prior knowledge of the pharmacokinetic profile of enalapril to account for the absorption distribution and elimination phases.

Calculated serum concentrations were assigned with a proportional error to imitate the case of typical errors occurring through analyzing the process for drug concentrations. For this step, R procedure “rnorm” was used to generate random numbers following a normal distribution around zero with a standard deviation (SD) of 30 percent. The R program is given in **Appendix 1, p. 102**.

2.2.1.1.3. Validation process

In the second step, the generated data for the validation step was fitted with the selected Bateman function specified in the predefined Phoenix® WinNonlin® (Certara) version 8 model library. The Gauss-Newton algorithm, with Levenberg and Hartley modifications, was used for iteration. Pharmacokinetic modeling of the generated data sets was performed using the least square minimization method in which model parameters were iterated to minimize the sum of squared residuals by applying weights on all fictive concentrations.[74,75] Different weighting schemes were analyzed, for instance, uniform weights using the ordinary least square minimization method were applied on all the concentrations to give equal importance in minimizing the sum of squares. Similarly, weighted least square and iterative reweighted least square minimization methods were analyzed by applying weights as reciprocal 1/y or squared of the reciprocal $1/y^2$ observed concentrations[76] and reciprocal 1/y or squared of the reciprocal $1/y^2$ predicted concentrations on all fictively generated concentrations respectively.[77]

The equations for the parameter iteration and minimization of OLS, WLS and IRLS objective functions are expressed in **equations 2-2, 2-3, and 2-4** respectively.

$$OLS(\Theta) = \sum (Yi - f(pi, \Theta)) \qquad \textbf{Equation 2-2}$$

$$WLS(\Theta) = \sum (Yi - f(pi, \Theta))^2 * W \qquad \textbf{Equation 2-3}$$

$$IRLS(\Theta) = \sum (Yi - f(pi, \Theta))^2 * PW \qquad \textbf{Equation 2-4}$$

Where the symbol $\sum$ *represents the sum of all individual observed concentrations* ***Yi****. The symbol* $f(pi, \Theta)$ *represents the concentrations* ***pi*** *predicted using the function* ***f*** *and iterated predicted parameters* Θ***, W*** *represents weights applied as 1/y or* $1/y^2$ *observed concentrations and* ***PW*** *represent weights applied as 1/y or* $1/y^2$ *predicted concentrations.*[78]

2.2.1.1.4. Comparing the iterated and reference pharmacokinetic parameters

Adequacy of the least square minimization method used in the validation process was evaluated by using typical validation characteristics namely accuracy and precision of the pharmacokinetics parameters calculated by writing an R program by using the following calculations;

$$\text{Relative error (\%)} = \frac{\text{iterated\_value}}{\text{reference\_value}} * 100 \qquad \text{Equation 2-5}$$

$$\text{Normalized parameter} = \frac{\text{iterated\_value}}{\text{reference\_value}} \qquad \text{Equation 2-6}$$

$$\text{Precision} = \frac{\text{SD (normalized parameter)}}{\text{mean (normalized parameter)}} * 100 \qquad \text{Equation 2-7}$$

$$\text{Accuracy} = \text{mean (relative error)} \qquad \text{Equation 2-8}$$

Accuracy and precision were chosen as desired statistical measures for evaluation, as proposed in the International Council for Harmonization (ICH) Harmonized Tripartite Guideline for Validation of Analytical Procedures and were evaluated in the light of the Food and Drug Administration guidelines for bioanalytical method validation. [79,80] It has to be considered that the FDA generally stated a replicate of samples or measurements that were necessary for these determinations, whereas the present evaluation was based upon the precision and accuracy of iterated values compared with generated values (as representatives for measured values), of the individual subjects of a fictive study population. The mean value of accuracy should be within 15% of the actual value and the precision at each concentration level should not exceed 15% of the coefficient of variation.[79]

2.2.1.2. Pharmacokinetic modeling analysis of the real data sets of enalapril

Pharmacokinetic modeling of the real data was performed based on the results obtained from the validation process. The most appropriate least-square minimization method according to the results of the simulated validation study was used.

2.2.1.2.1. Trial design and source data of enalapril serum concentrations

Data were generated from a phase I clinical trial with a publically outlined design and part of the LENA project (labeling of enalapril from neonate to adolescence, European Union Seventh Framework Program (FP7/2007-2013) under the grant agreement no 602295). Approval for the trial protocol was given by the independent Ethics Committee of the University Hospitals KU Leuven and the study was conducted in accordance with the International Council on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice.[69] In brief, the pharmacokinetic modeling analysis has been the second step using the measured concentration of enalapril where twenty-four healthy male and female volunteers had been included in an open-label, randomized crossover, three treatment, three-period study. Blood samples were taken at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 48 hours after administration of the drug. Treatment A contained two reference tablets each of 5 mg strength swallowed with 240ml of water. Treatment B consisted of ten ODMTs each of 1mg strength, swallowed with 240ml of water. Treatment C consisted of ten ODMTs each of 1mg strength dispersed on the tongue following wetting of the mouth with 20ml of water in fasting state. Treatment C was kept in the mouth for some time before swallowing to account for any trans-mucosal absorption. Subject number 5 of treatment A was pointed out as an outlier and follows an unusual double peak with an unusually delayed tmax of around 4 hours. Application of the Wagner Nelson method found that after 3 hours of drug administration, only 30 percent of the drug was absorbed compared to the 95-100 percent of the drug absorbed in almost all other subjects. Therefore, subject number 5 was excluded from the main pharmacokinetic modeling analysis. For treatment A, subject number 17 did not continue the trial and was removed from the analysis.

2.2.1.2.2. Bioanalytics of enalapril serum samples

Serum and urine concentrations of enalapril and enalaprilat were measured using methods validated according to EMA and FDA guidelines through liquid chromatography

triple quadrupole tandem mass spectrometry. The details of the bioanalytical method have been published in the literature.[81]

2.2.1.2.3. Software used and pharmacokinetic modeling

Phoenix® WinNonlin® version 8 was used for the nonlinear regression analysis. The data were fitted with the one and two-compartment models, with and without incorporating a lag time of absorption, with the 1st order of absorption and elimination. Both models were analyzed based on goodness of fit plots including, time versus log and linear observed and predicted plots, observed versus predicted plots and residual versus predicted plots. Information from the validation step was used to select the least square minimization method, which predicts the most accurate, and precise model parameters. Initial parameters were generated using an inbuilt curve stripping and grid search method of Phoenix® WinNonlin®. Upper and lower bounds were applied to the initial parameter values.

2.2.1.2.4. Descriptive and inductive statistics

Descriptive statistics, including the calculation of geometric mean, standard deviation, % coefficient of variation of the pharmacokinetic parameters iterated for each treatment, was performed using Phoenix® WinNonlin®. An R program was written for a two-sided paired t-test on the log-transformed pharmacokinetic parameters with p=0.05 as the level of significance to evaluate the statistically significant differences between the pharmacokinetic parameters of treatment A, B and C iterated for each individual.

2.3. Results

2.3.1. Selection of the least square minimization method

Weighting scheme, using reciprocal of the squared predicted concentration $1/y^2$ (IRLS minimization method) predicted all pharmacokinetic model parameters of the Bateman function, i.e. volume of distribution, rate constants of absorption and elimination, within the acceptable mean accuracy range of 15% specified by the FDA **Table 2-2**. Especially, the percent inaccuracy of rate constants of absorption was 0.15% while no weighting schemes were able to predict rate constants of absorption values in the acceptable accuracy range.

Table 2-2 Accuracy and Precision of pharmacokinetic model parameters for 100 virtual subjects after the one-compartmental model analysis with different weighting schemes.

Weights	VD		KA		KE	
	%Accuracy	%Precision	%Accuracy	%Precision	%Accuracy	%Precision
$1/y^2$ pred	-2.360	14.11	0.148	40.26	1.402	8.385
1/y pred	0.499	20.69	23.14	84.36	1.399	15.68
$1/y^2$ obs	27.46	33.60	55.67	84.00	0.850	18.55
1/y obs	6.522	27.37	16.51	63.45	10.30	28.66
Uniform	-1.320	33.33	53.15	122.33	14.09	39.59

Abbreviations: pred, predicted; obs, observed; Vd, apparent volume of distribution; KA, rate constant of absorption; KE, the rate constant of elimination.

Similarly, the weighting scheme applied as reciprocal of the squared predicted concentration ($1/y^2$ pred) iterated the most precise pharmacokinetic parameters as compared to all other weighting schemes. The precision of VD and KE parameters were within the FDA specified precision range of 15%

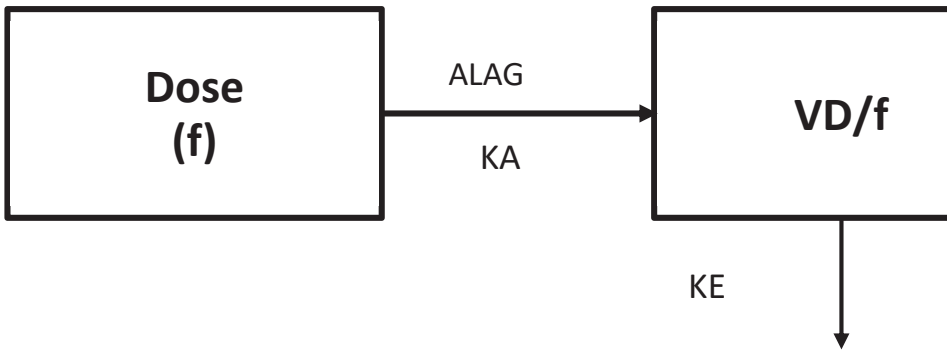


Figure 2-2 Schematic diagram of the one compartmental model used for the generation of 100 virtu of simulated data and real data of enalapril from the reference and developed orodispersible mini absorbed into the central compartment with a delay (ALAG) and absorption rate constant (KA). The distribution of (VD/f) and eliminated with a rate constant KE.

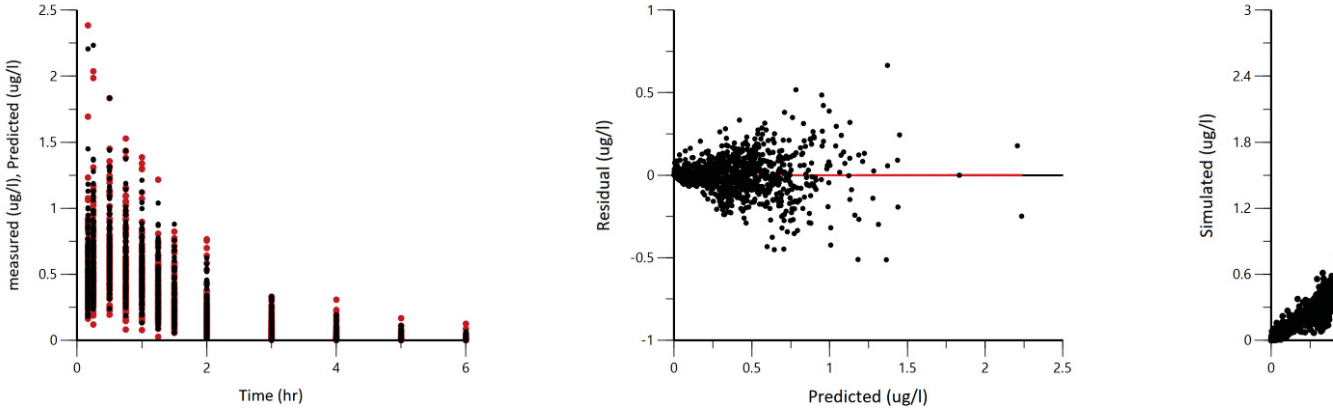


Figure 2-3 Goodness of fit plots obtained after the application of the one-compartment model and method to the 100 simulated dataset.

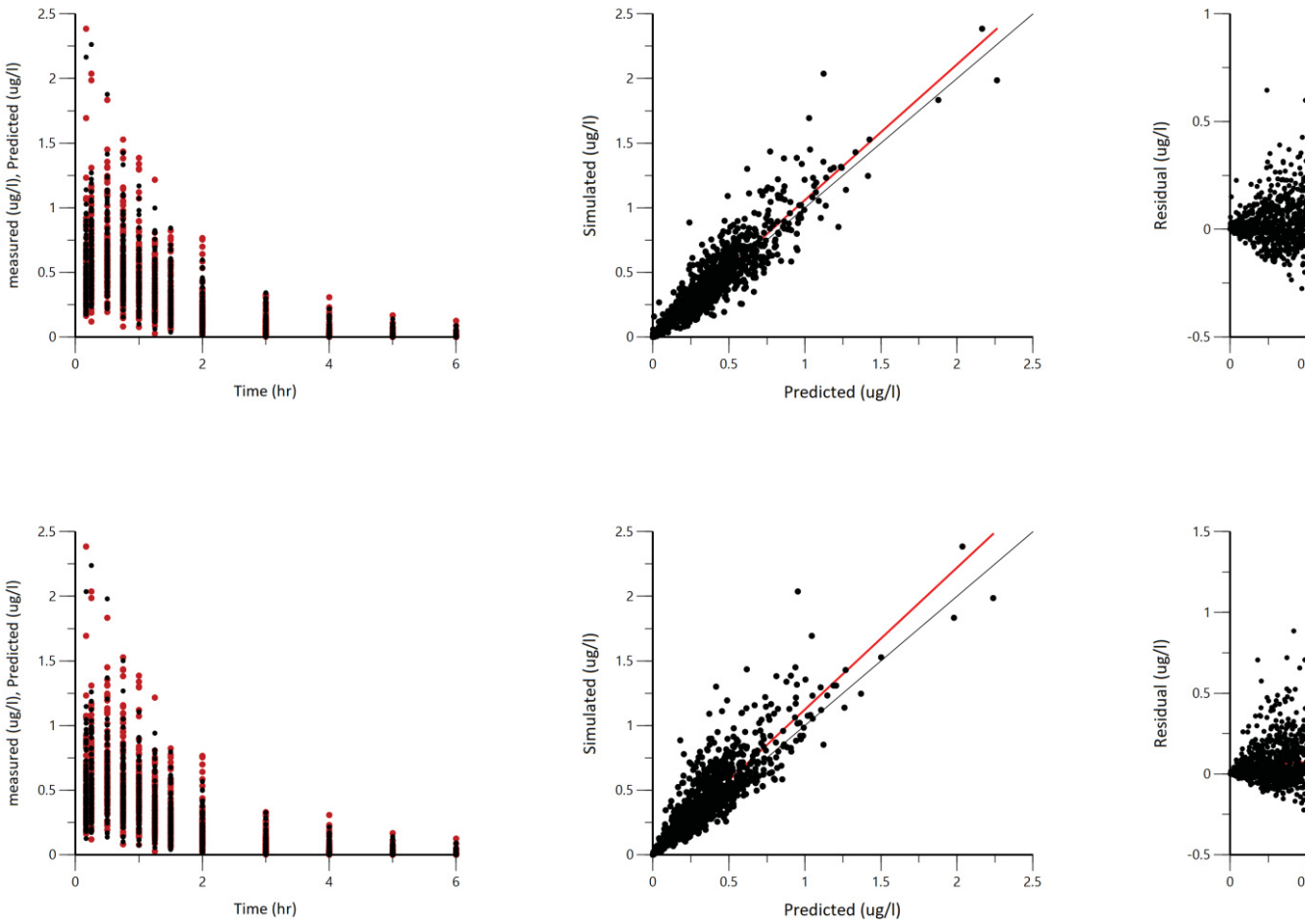


Figure 2-4 Goodness of fit plots obtained after the application of the one-compartment model and we method using 1/y observed (first row) and $1/y^2$ observed (second row) weighting scheme.

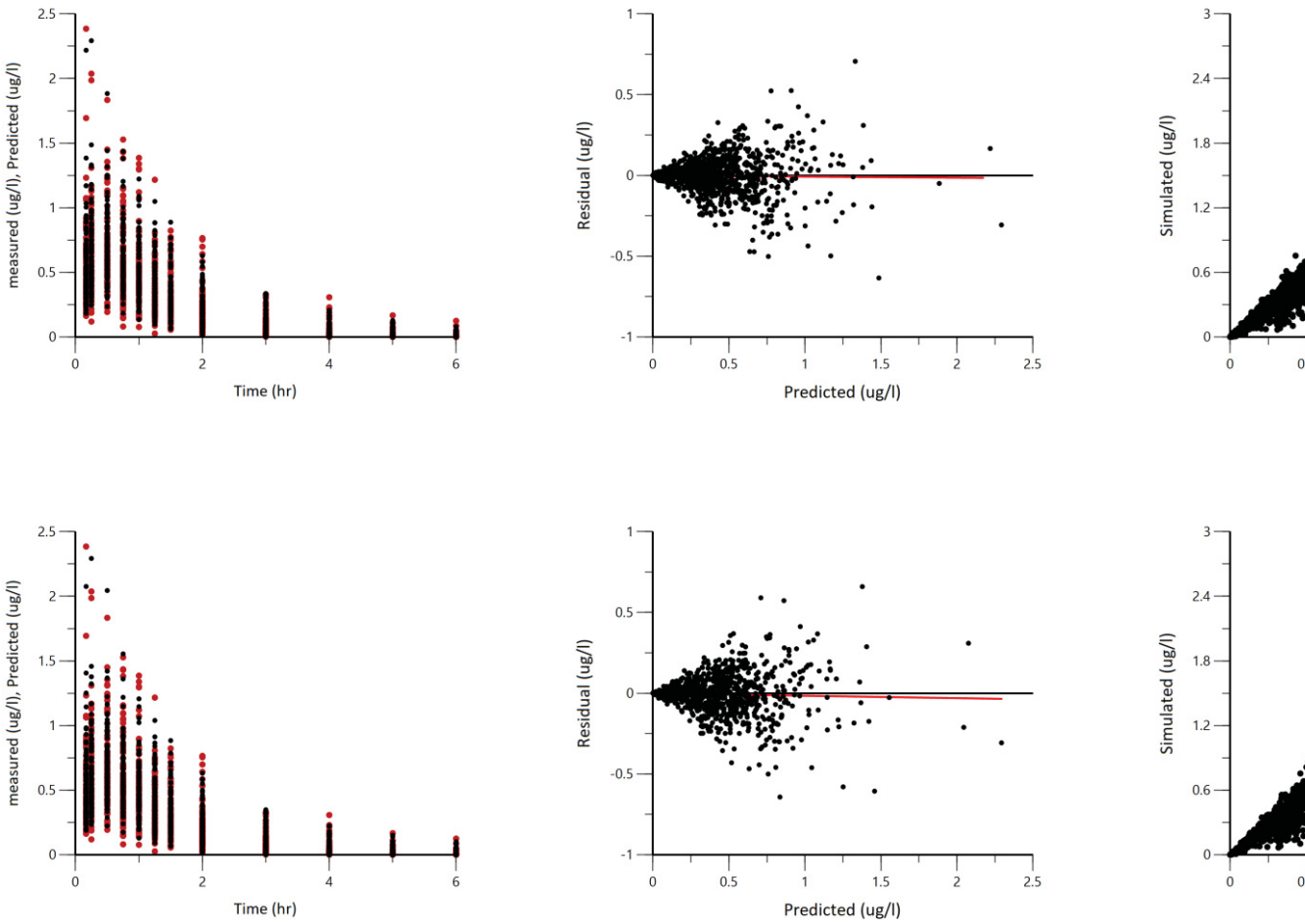


Figure 2-5 Goodness of fit plots obtained after the application of the one-compartment model and ite
minimization method using 1/y predicted (first row) and $1/y^2$ predicted (second row) weighting scheme.

However, the precision of KA was calculated to be 40% and was much higher than the specified limits. This may be due to the inclusion of less number of fictive time points of sampling in the absorption phase during the fictive data generation, which was not sufficient to iterate a precise value of KA for each subject. Still, weighting by the reciprocal of the squared predicted concentration resulted in lower imprecision compared to the accuracy calculated using other weighting schemes as summarized in **Table 2-2**.

Ordinary least square minimization method resulted in the lowest sum of square residual value as summarized in **Table 2-3**. However, the method produced the least precise and less accurate pharmacokinetic parameters compared to other weighting schemes.

Table 2-3 Mean sum of the squared residuals (SSR) and the weighted sum of square (WSSR) values obtained after model analysis of 100 virtual profiles with different weights

Weights	SSR	WSSR
$1/y^2$ pred	0.16	0.81
1/y pred	0.14	0.25
$1/y^2$ obs	0.25	1.10
1/y obs	0.16	0.30
Uniform	0.13	0.13

Abbreviations: SSR, the sum of squared residual; WSSR, a weighted sum of squared residual; obs, observed; pred, predicted; obs, observed.

Therefore, accuracy and precision, not the sum of the squared residual values were used in the selection of the appropriate LSMM for modeling of the real data set. Model performance for fitting the simulated data sets can be visualized using the goodness of

fit plot in **Figure 2-6**, which shows that the model and weighting scheme adequately predicted the simulated data.

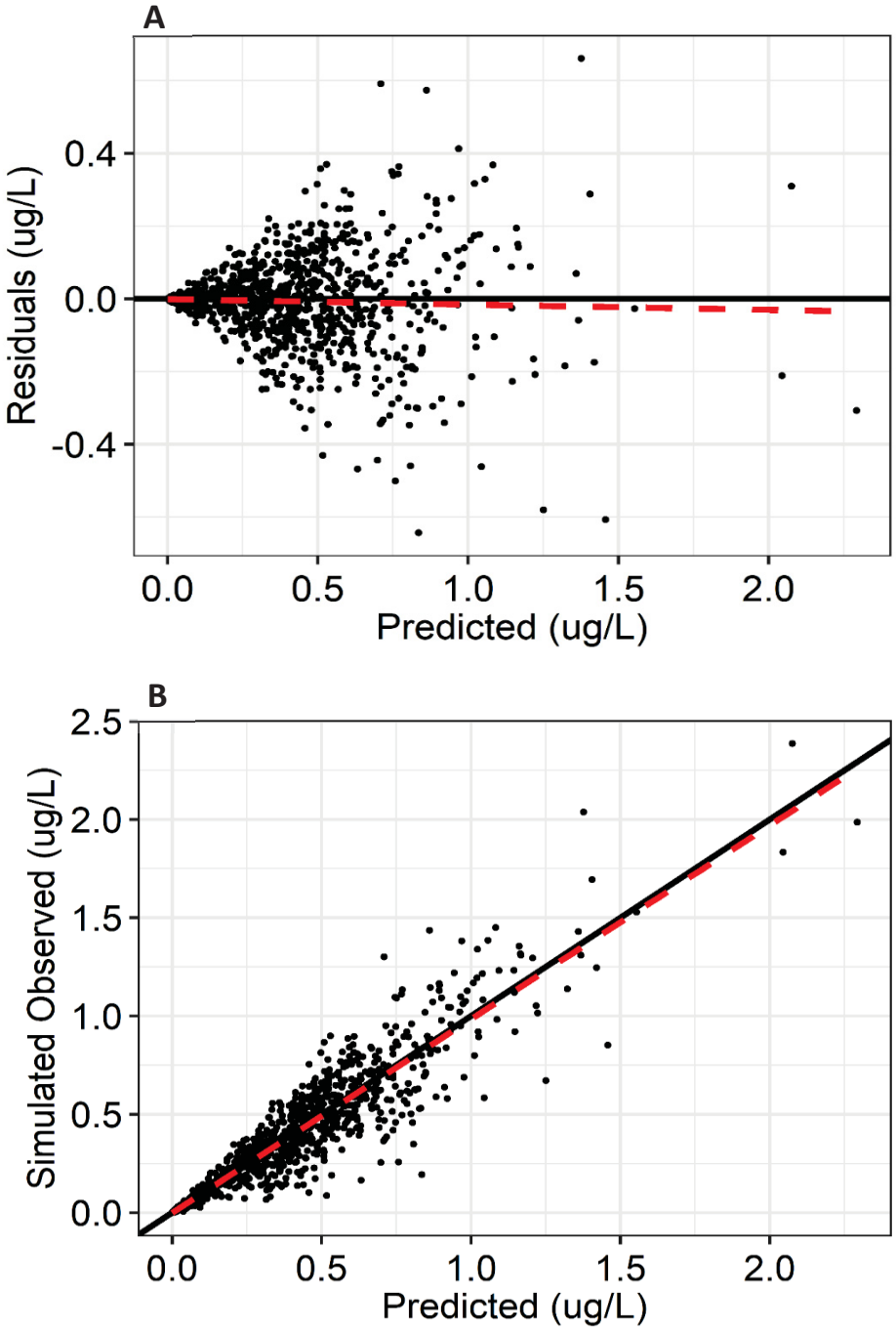


Figure 2-6 Goodness of fit plot including residual vs predicted (A) concentrations plot of simulated fictive profiles and simulated observed concentration data vs predicted (B) plot obtained after the one-compartment model analysis and $1/y^2$ predicted weighting scheme. The red dashed line represents the regression line and the solid black line starting from zero represents the identity line.

2.3.2. Pharmacokinetic modeling analysis of the enalapril real data

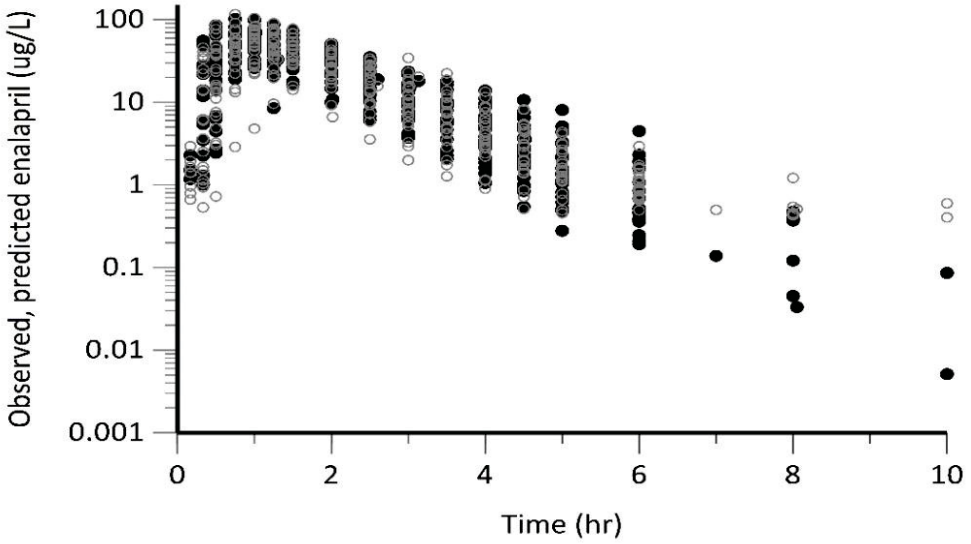
The One-compartment model with the 1st order of absorption and elimination and an incorporated lag time adequately predicted the absorption, distribution and elimination phases of enalapril time vs concentration profiles of the three treatments.

The model was not adequate to predict few lower concentrations at the onset of absorption and the elimination phases as shown in **Figure 2-7**. A two-compartment model was able to predict those few concentrations but as the one-compartment model predicted most of the concentrations of pharmacokinetic profiles of treatment A, B and C as shown in **Figure 2-8, Figure 2-9**, and **Figure 2-10** respectively, therefore, using the two-compartment model will result in over parametrization and was not selected as our final model. The two-compartment model also resulted in higher standard errors compared to the one-compartment model and gave more confidence to select the one-compartment model for the modeling of enalapril data.

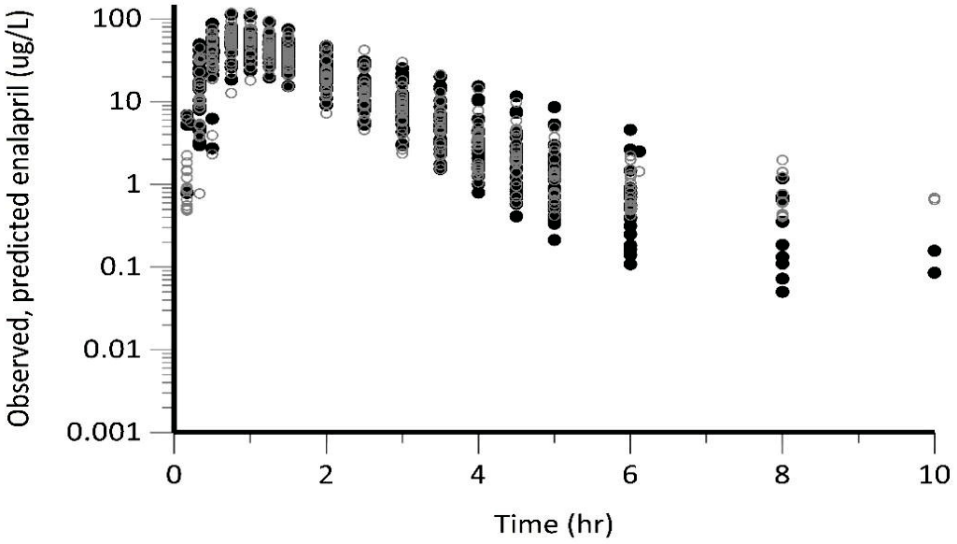
Visual inspection of individual plots shows that the model was not adequate to predict few lower concentrations in the onset of absorption and the terminal phase of elimination of some subjects. Therefore, higher weights were applied using reciprocal of the predicted concentrations (1/y pred) instead of reciprocal of square predicted ($1/y^2$ pred) concentration on all observed concentrations.

Observed vs predicted concentration plots show the model performance where observed and predicted concentrations agree around the regression line to each other. Furthermore, the identity line was also near to the regression line as shown in **Figure 2-11**. Residual vs predicted plots show almost equal spread of residuals along the positive and negative sides and show that the model performed well in predicting the observed enalapril concentrations. **Table 2-4, Table 2-5,** and **Table 2-6** represent the pharmacokinetic parameters of each individual and the descriptive statistics for all patients administered treatment A, B, and C respectively. The geometric mean value, percent coefficient of variation, minimum and maximum values were calculated and included in these tables.

A


Observed, predicted enalapril (ug/L)
100
10
1
0.1
0.01
0.001
0
2
4
6
8
10
Time (hr)

B


Observed, predicted enalapril (ug/L)
100
10
1
0.1
0.01
0.001
0
2
4
6
8
10
Time (hr)

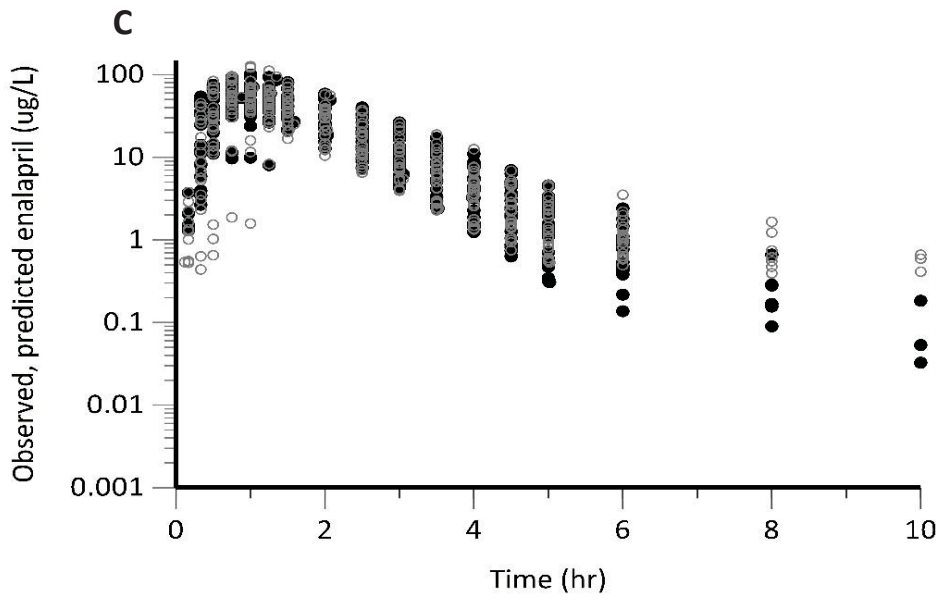


Figure 2-7 Semi-log time versus observed and predicted concentration plot of enalapril showing individual predictions for treatment A, B, and C. The grey open circles represent the observed concentrations and the black filled circles represent the predicted concentrations.

The **Table 2-7** summarizes the results of pharmacokinetic model parameters obtained from pharmacokinetic modeling for the three treatment arms of enalapril. The individual pharmacokinetic parameters were subjected to descriptive statistics to calculate the population geometric mean values for the model parameters and coefficient of variation values describing the variability of the parameter in the population.

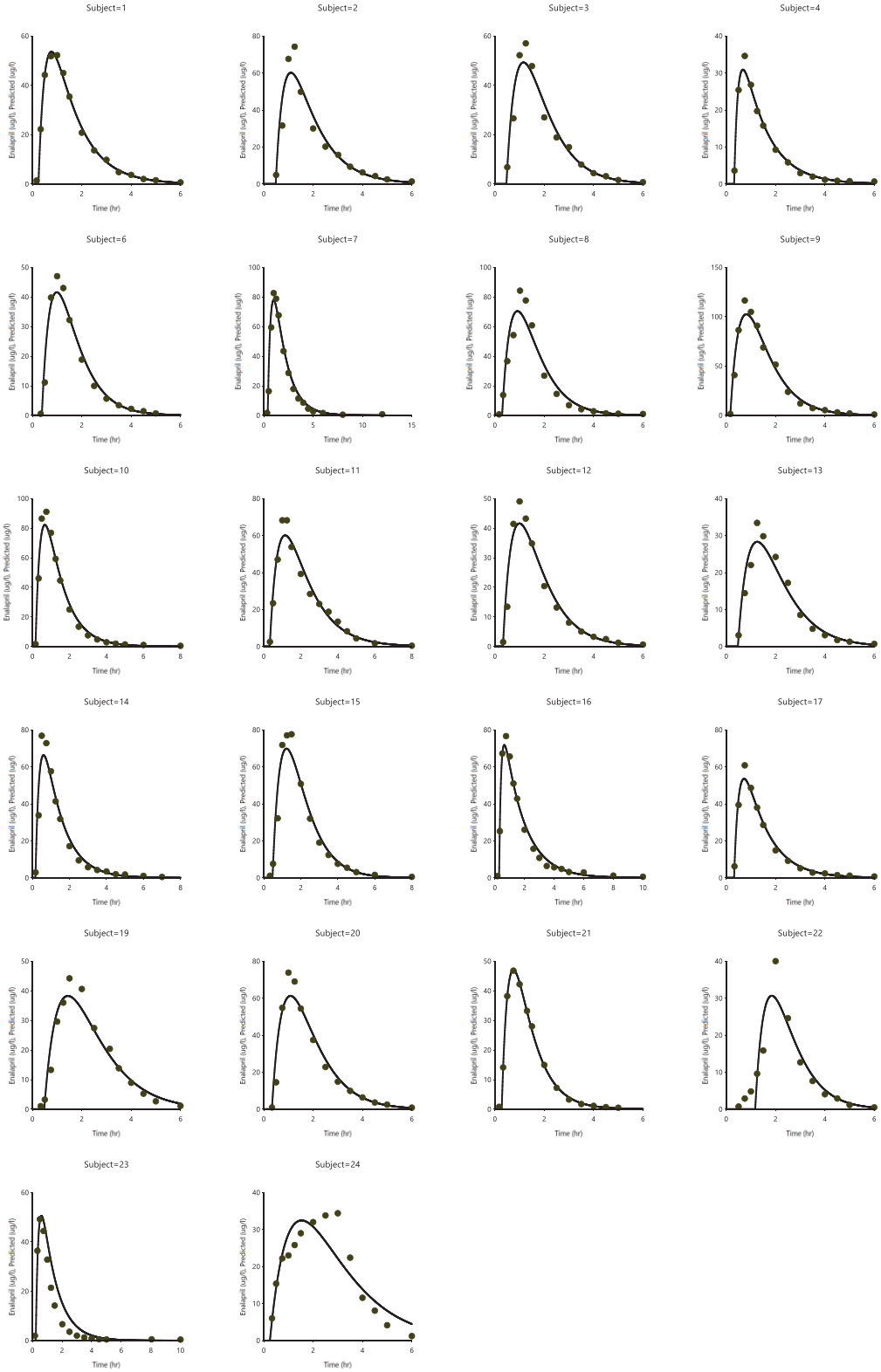


Figure 2-8 Treatment A time vs linear observed and predicted concentration plots of enalapril, analyzed using the one-compartment model and 1/y pred weighting scheme. The dots represent the observed concentrations and the continuous solid line represents the predicted concentrations.

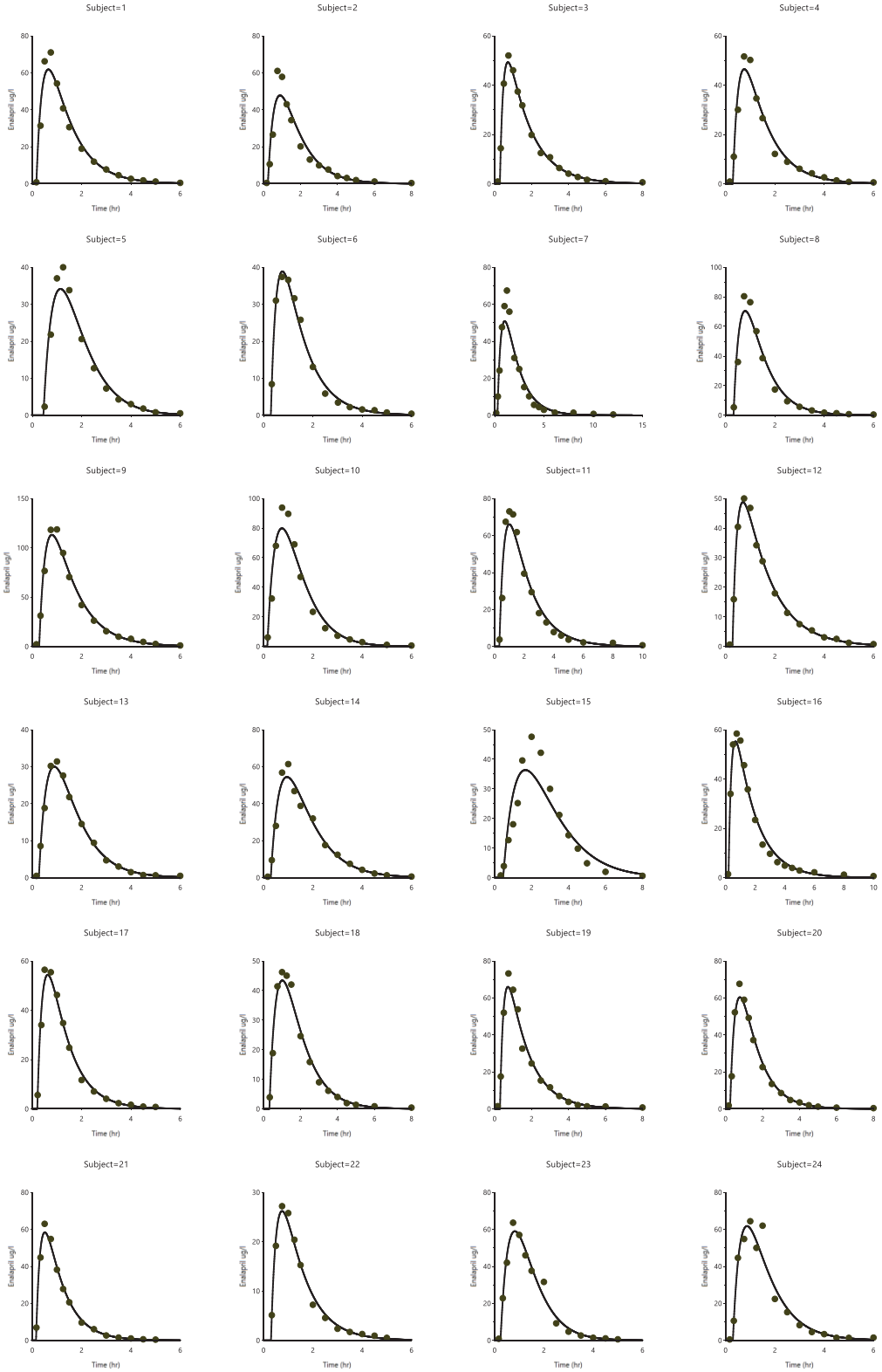


Figure 2-9 Treatment B time vs linear observed and predicted concentration plots of enalapril, analyzed using the one-compartment model and 1/y pred weighting scheme**.** The dots represent the observed concentrations and the continuous solid line represents the predicted concentrations.

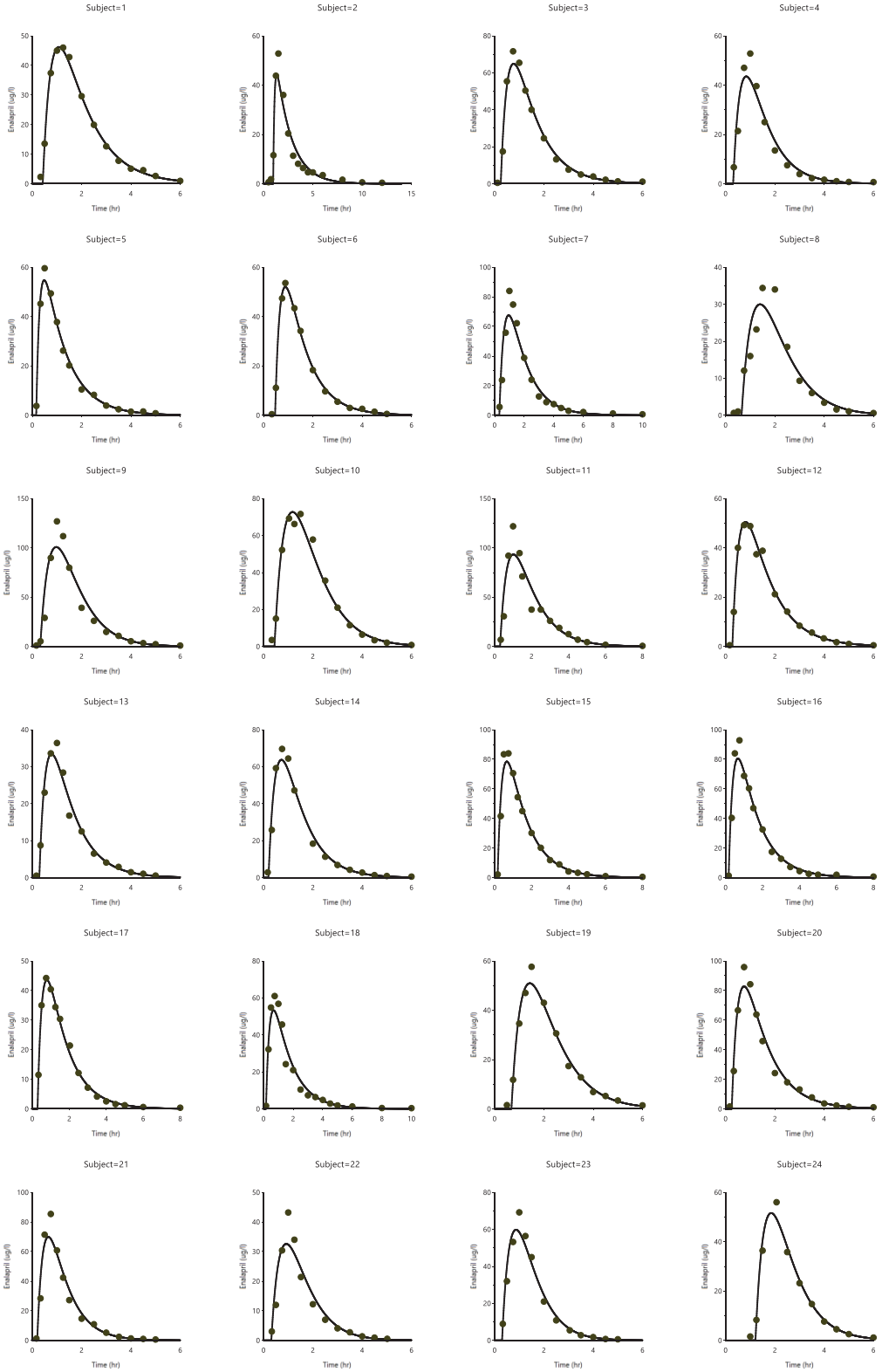


Figure 2-10 Treatment C time vs linear observed and predicted concentration plots of enalapril one-compartment model with 1/y pred weighting scheme**.** The dots represent the observed concentrations and the continuous solid line represents the predicted concentrations.

Table 2-4 Descriptive statistics of final pharmacokinetic parameters of treatment A obtained after one-compartment model analysis with 1/y predicted weighting scheme.

Subject	VD/f (l)	KA (1/hr)	KE (1/hr)	tlag (hr)
1.00	86.48	3.34	0.95	0.24
2.00	70.27	2.54	0.97	0.48
3.00	44.44	1.14	1.81	0.47
4.00	173.83	6.08	0.99	0.32
6.00	57.97	1.42	1.91	0.38
7.00	60.75	2.99	0.80	0.40
8.00	44.66	1.80	1.43	0.29
9.00	31.15	1.75	1.34	0.16
10.00	53.98	3.29	1.08	0.16
11.00	65.49	1.72	0.80	0.32
12.00	49.95	1.12	1.95	0.33
13.00	98.35	1.26	1.29	0.47
14.00	74.32	4.38	1.00	0.16
15.00	47.03	1.56	1.12	0.47
16.00	82.34	7.27	0.73	0.28
17.00	92.71	4.77	1.07	0.32
19.00	73.92	1.05	1.03	0.48
20.00	47.52	1.37	1.28	0.33
21.00	86.36	3.15	1.34	0.28
22.00	88.01	1.43	1.55	1.17
23.00	145.08	9.59	0.96	0.26
24.00	85.50	0.77	0.79	0.25
N	22	22	22	22
Geometric Mean	69.675	2.275	1.143	0.328
CV% Geometric Mean	41.79	77.99	29.24	46.57
SD Log	0.4012	0.6893	0.2864	0.4431
Min	31.15	0.77	0.73	0.16
Max	173.83	9.59	1.95	1.17

Table 2-5 Descriptive statistics of final pharmacokinetic parameters of **treatment B** obtained after one-compartment model analysis with **1/y predicted** weighting scheme.

Subject	VD/f (l)	KA (1/hr)	KE (1/hr)	tlag (hr)
1.00	73.99	3.54	1.05	0.16
2.00	86.86	2.32	0.93	0.23
3.00	110.08	5.09	0.79	0.29
4.00	100.54	3.82	1.06	0.29
5.00	82.67	1.45	1.43	0.45
6.00	116.80	3.66	1.11	0.30
7.00	87.03	2.48	0.66	0.29
8.00	57.24	3.13	1.35	0.32
9.00	39.89	3.29	1.02	0.28
10.00	40.09	1.93	1.47	0.15
11.00	71.95	2.69	0.70	0.32
12.00	107.95	4.96	0.88	0.28
13.00	125.12	2.19	1.14	0.27
14.00	69.73	2.10	1.07	0.29
15.00	77.82	0.84	0.83	0.47
16.00	98.85	4.71	0.71	0.20
17.00	83.87	4.06	1.22	0.20
18.00	86.05	1.93	1.02	0.31
19.00	79.45	4.88	0.88	0.29
20.00	72.86	3.08	1.04	0.24
21.00	81.76	5.11	1.32	0.15
22.00	177.70	3.94	1.10	0.30
23.00	48.05	1.74	1.71	0.24
24.00	66.03	2.61	1.09	0.30
N	24	24	24	24
Geometric Mean	80.506	2.882	1.037	0.266
CV% Geometric Mean	35.34	47.78	24.45	28.84
SD Log	0.3431	0.4535	0.2409	0.2827
Min	39.89	0.84	0.66	0.15
Max	177.70	5.11	1.71	0.47

Table 2-6 Descriptive statistics of final pharmacokinetic parameters of treatment C obtained after one-compartment model analysis with 1/y Pred weighting scheme.

Subject	VD/f (l)	KA (1/hr)	KE (1/hr)	tlag (hr)
1.00	93.06	2.42	0.87	0.42
2.00	136.78	7.38	0.64	0.97
3.00	67.64	3.14	1.06	0.25
4.00	91.16	2.72	1.23	0.31
5.00	98.65	6.75	1.07	0.16
6.00	90.52	4.32	1.17	0.47
7.00	67.23	2.73	0.83	0.32
8.00	94.72	1.34	1.32	0.65
9.00	31.04	1.72	1.38	0.32
10.00	38.67	1.36	1.36	0.44
11.00	42.41	2.01	0.92	0.30
12.00	89.75	3.19	0.98	0.27
13.00	131.69	3.30	1.11	0.28
14.00	64.72	2.89	1.18	0.20
15.00	62.71	3.83	0.88	0.16
16.00	61.00	3.78	0.88	0.16
17.00	111.71	3.72	0.90	0.28
18.00	94.17	3.82	0.82	0.16
19.00	69.12	1.70	1.04	0.68
20.00	54.57	3.39	1.05	0.25
21.00	59.20	3.37	1.36	0.20
22.00	91.33	1.74	1.55	0.31
23.00	46.52	1.74	1.78	0.30
24.00	66.19	1.92	1.26	1.21
N	24	24	24	24
Geometric Mean	72.460	2.800	1.081	0.322
CV% Geometric Mean	38.96	47.44	23.70	59.08
SD Log	0.3759	0.4506	0.2337	0.5472
Min	31.04	1.34	0.64	0.16
Max	136.78	7.38	1.78	1.21

Table 2-7 Geometric mean and geometric coefficient of variation values of enalapril pharmacokinetic parameters for treatment A, B, and C.

Parameters	VD/f (L)	KA (1/h)	KE (1/h)	tlag (h)
Treatment A				
Geo Mean	69.675	2.275	1.143	0.328
Geom.CV%	44.0	78.7	30.1	57.0
Treatment B				
Geo Mean	80.506	2.882	1.037	0.266
Geom.CV%	34.8	39.5	24.2	27.6
Treatment C				
Geo Mean	72.460	2.800	1.081	0.322
Geom.CV%	35.5	48.7	23.6	68.8

Abbreviations: Geo Mean, geometric mean value of all subjects; CV%, percent coefficient of variation; VD/f, apparent volume of distribution; KA, rate constant of absorption; KE, rate constant of elimination; f, fraction of drug absorbed; tlag, delay time in absorption.

Overall, model performance can be seen in **Figure 2-12**, which indicates the simulation results, where the observed data were in the range of standard deviation of the mean profile of simulated profiles. The model adequately predicted the individual time versus observed concentration profiles of the three treatment arms as shown in **Figure 2-11**.

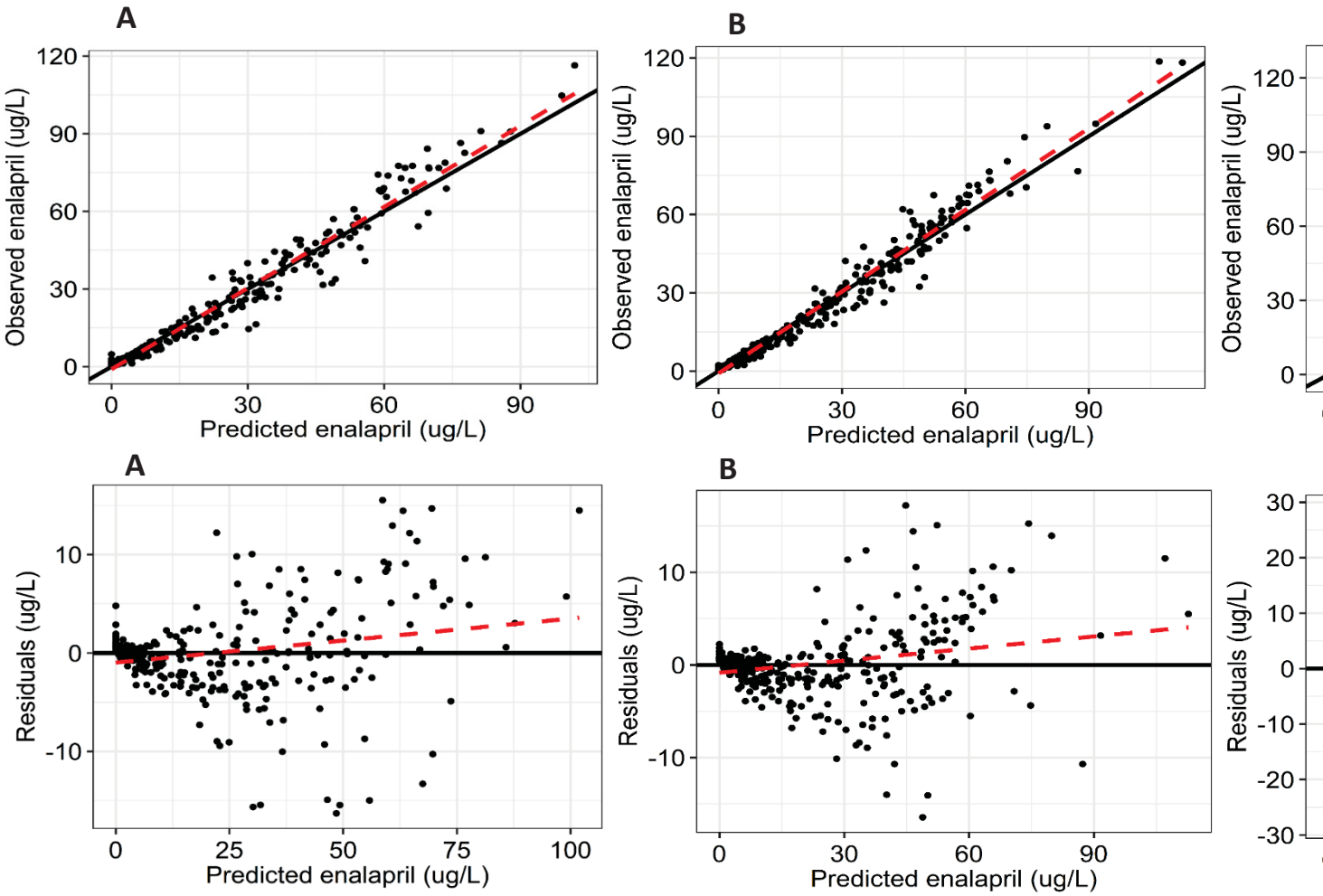


Figure 2-11 Residual vs predicted concentration plot of enalapril for treatment A, B, and C respectively aft
model and iteratively reweighted least square minimization method of parameter estimation. The dashed
black solid line represents the identity line.

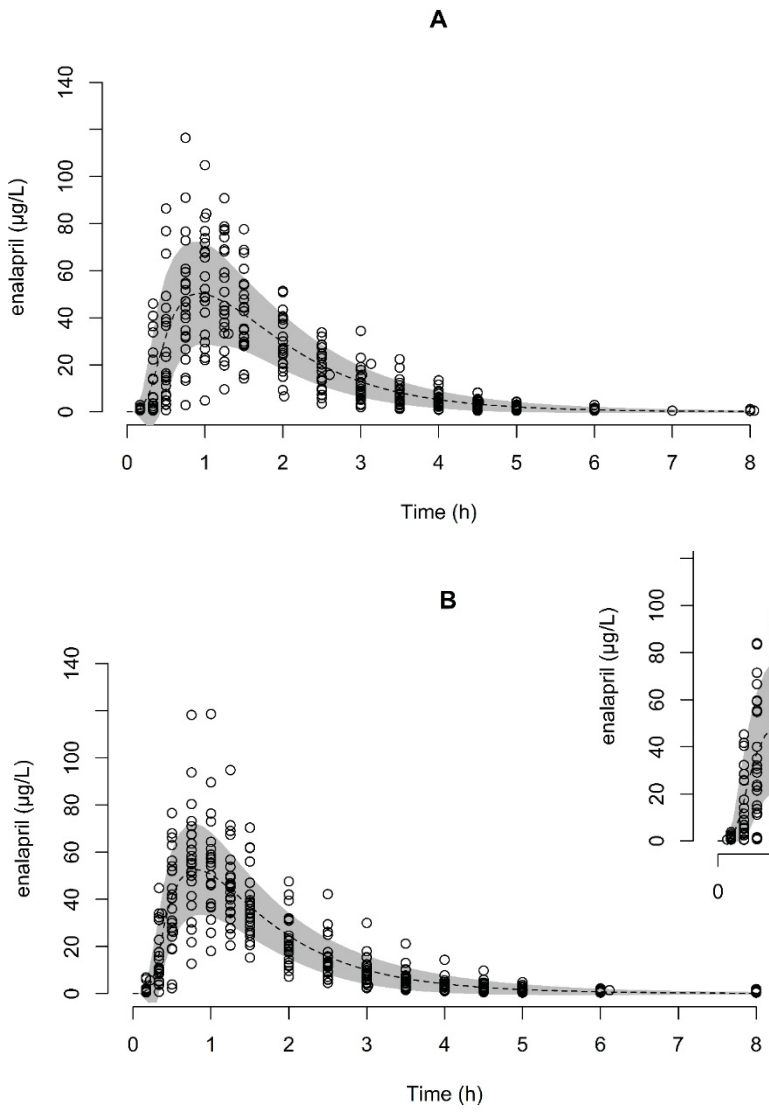
The mean time taken for the drug to appear in blood was 16 minutes from ODMT administered with 240 ml water compared to 20 minutes from reference tablets. This means that enalapril appeared 4 minutes earlier after ODMT administration if compared to the administration of reference formulation.

Table 2-8 Results (p values) of the paired t-test for the comparison of pharmacokinetic parameters of the three treatments. *P-value for the level of significance is less than 0.05.

Parameter	Test: A vs. B	Test: B vs. C	Test: A vs. C
KA (1/h)	0.078	0.836	0.258
VD/f (L)	0.100	0.098	0.744
KE (1/h)	0.119	0.316	0.500
tlag (h)	0.018*	0.172	0.744

Abbreviations: VD/f, apparent volume of distribution; f, fraction of dose absorbed; KA, rate constant of absorption; KE, rate constant of elimination; tlag, delay time in absorption; A, reference treatment A; B, treatment B; C, treatment C.

The box plots given in **Figure 2-13** show the distribution of pharmacokinetic model parameters from minimum to maximum values, medians, and quartiles ranges. It can be seen that the distribution of the model parameters overlaps each other and their median and mean values are in close agreement with each other.



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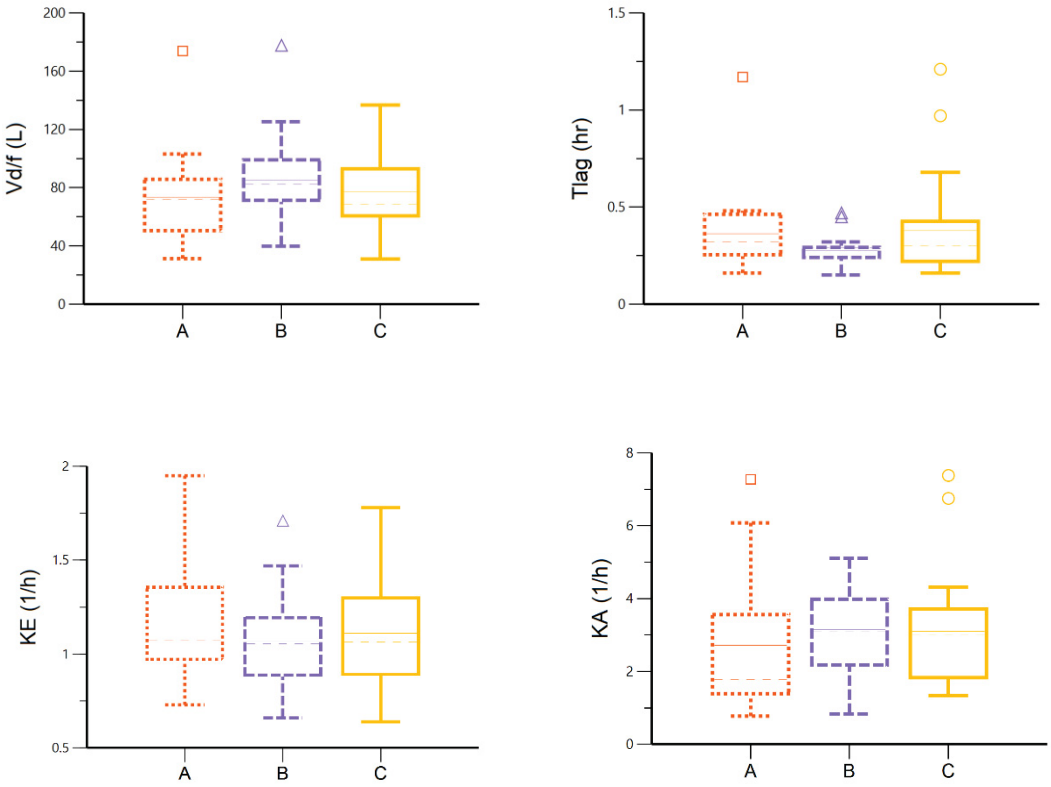


Figure 2-13 Box plot analysis of pharmacokinetic parameters iterated using 1 compartment model and 1/y predicted weighting scheme for enalapril treatment A, B, and C. The dashed line in the box represents the median value solid lines in the box represent mean values.

2.4. Discussion

A pharmacokinetic model-dependent approach revealed that orodispersible mini-tablets show a 4 minutes earlier appearance of enalapril in the systemic circulation than the conventional tablets. The model-dependent approach also showed that the rate constant of absorption, the volume of distribution and the rate constant of elimination were not different if ODMTs and conventional tablets were compared. The modeling approach was substantiated by a validation study, which validated the pharmacokinetic software by iterating accurate and precise model parameters. The validation study showed a weighting scheme applied as reciprocal of the squared predicted concentration iterated the most accurate and precise model parameters. However, as the model was not able to predict few lower concentrations at the absorption phase, higher weights were applied using reciprocal of the predicted concentration.

The simulated validation step estimated weighting scheme applied as reciprocal of squared predicted concentration in a reiterative manner iterate the most accurate and precise model parameters. No other weighting scheme estimated precise parameters. Although the uniform weighting scheme iterated the lowest sum of square value, yet the parameters iterated were highly imprecise. Therefore, the sum of square residual value was found to be a bias parameter. Iteratively reweighted least square minimization method was proved to be the most appropriate parameter estimation method and the results were in line with the preference and recommendations given in the literature to use iteratively reweighted least square minimization method for pharmacokinetic modeling analysis.[77,78]

One compartment model adequately fit the time versus enalapril observed concentration profiles. The Two-compartment model was also tested but it resulted in higher standard errors and therefore simpler one-compartment model was used for the pharmacokinetic modeling analysis. Visual enalapril time vs concentration plots given in the literature suggests that the one-compartmental model shall be the most appropriate pharmacokinetic model for enalapril after oral administration.[82,83]

The statistical paired t-test suggested only a significant difference in the lag time parameter, which showed an early appearance of drug in blood after the administration of ODMT with 240 ml water compared to reference tablets. This may be linked to the fast disintegration and dissolution which depends on the exposed surface area of ODMTS in the gastrointestinal tract preceding drug absorption.[38] As 10 ODMTs of 1 mg strength administered with 240 ml water provide a larger surface area compared to two 5 mg reference tablets, higher dissolution rates were expected from the ODMTs.[36] However, no difference in the lag time of absorption observed between the orodispersed ODMTs with 20 ml water and the reference formulation suggested no or very minute transmucosal absorption of the drug. The model-dependent approach was able to inform about the transmucosal absorption of the drug from the real dataset without conducting expensive and time consuming *in-vitro in-vivo* translational studies.

The rate constant of absorption is influenced by the disintegration and dissolution rates, therefore, formulation design can affect the speed of release or absorption of the drug.[84,85] However, as enalapril is a BCS class III drug[86,87] and the absorption of BCS class III drugs depends on the permeability of the drug substance across the intestinal membrane which remains the same if the permeability is not enhanced.[84] As enalapril was administered to the same individuals, the permeability of drugs should remain the same and similar rate constants of absorption were expected as were predicted by the pharmacokinetic model for the three treatments. Previously, no such model-dependent pharmacokinetic comparison of rate and delay in absorption of the drug was reported.
The volume of distribution of the drug is dependent on the elimination rate constant which depends on the status of physiological eliminating organs such as liver and kidney function.[84] As in the present analysis, each of the three treatments was administered in 3 separate periods to the same healthy individuals, the same rate constant of elimination and apparent volume of distribution values in each subject was found by the applied pharmacokinetic modeling. Since the apparent volume of distribution is not different between the three treatments administered to the same individuals, the same value for pharmacokinetic parameter VD/f indicates no difference in bioavailability between the three treatment arms. While this chapter deals with the pharmacokinetic

analysis of the parent prodrug enalapril administered using different treatments modalities, further detailed population pharmacokinetic analysis of enalapril and its pharmacologically active metabolite enalaprilat in serum and urine has been carried out in chapter 3 to explain the complete absorption and disposition of the drug and metabolite.

2.5. Conclusion.

In conclusion, the validated accurate and precise iteratively reweighted least square minimization method and the one-compartment model adequately predicted the pharmacokinetics of enalapril in the developed and reference formulations. The comparison of pharmacokinetics in the three formulations revealed an early absorption of enalapril from ODMT administered with 240 ml water compared to the reference formulation. No or very limited transmucosal absorption of the drug was observed from the dispersed ODMT treatment of enalapril.

Chapter 3

Population pharmacokinetic modeling analysis of the serum and urine concentrations to account the absorption and disposition of enalapril and enalaprilat from reference and orodispersible mini-tablets.

3.1. Introduction

Enalapril is a prodrug, which is converted in the liver by the action of carboxylesterases enzyme into its active metabolite enalaprilat. Enalapril itself has a mild antihypertensive effect while enalaprilat is a potent ACE inhibitor.

The comparative pharmacokinetic modeling analysis in Chapter 1 has revealed a 4-minute difference in the onset of enalapril absorption when administered using orodispersible mini-tablets compared to the reference formulation. The regulatory authorities require the comparison of bioavailability and pharmacokinetics of the prodrug from the developed and reference formulations.[28] However, the pharmacological basis enalaprilat pharmacokinetics will be useful to determine the difference in the onset and magnitude of angiotensin-converting enzyme inhibitory effect. In addition, the availability of the urine data of enalapril and enalaprilat will determine the complete pharmacokinetics of the drug and metabolite right from its administration until its elimination.

A population pharmacokinetic modeling approach using nonlinear mixed effect modeling analysis and maximum likelihood method of parameter estimation is commonly used to account for the pharmacokinetics of the prodrug and the formed metabolite in a simultaneous semi mechanistic modeling approach.

3.1.1. Non-Linear Mixed Effect Model development

The simultaneous semi-mechanistic population pharmacokinetic modeling analysis was conducted using the nonlinear mixed effect modeling approach implemented through NONMEM software by Dr. Lewis B. Sheiner and Dr. Stuart L. Beal and further supported by Alison J. Boeckmann. Compared to the least square minimization method, the nonlinear mixed effect modeling approach fits the model to the whole data at once and estimates the model parameters and its variability in the population.

Component of nonlinear mixed effect models includes the mathematical function, different levels of variabilities and independent variables like time, dose, weight, etc.

3.1.1.1. Mathematical component of the Non-Linear Mixed Effect Models

The mathematical component of the nonlinear mixed effect model contains fixed effect parameters, which are the structural part of the model and represent the typical population mean value of a parameter. For instance, the volume of distribution, clearance, the rate constant of absorption, etc. In NONMEM, these parameters are coded as THETA vectors. The nonlinear mixed effect models are developed in a stepwise manner starting with the development of a structural model.

3.1.1.2. Statistical part of the nonlinear mixed effect models

The statistical part of the nonlinear mixed effect model constitutes different levels of variability that are based on some assumptions of the normal distribution of parameters with a mean of 0 and variance describing the distribution of individual parameter value around the central tendency to explain the distribution of variability of the parameters in the population. These parameters are also termed as random variability parameters. Two levels of random effects are introduced in the nonlinear mixed effect models to account for the random unexplained variability.

a. Level 1 random effects

The level 1 random effect introduces the between-subject variability into the model and account for the differences in the magnitude of the individual parameter from the typical parameters. Between subject variability is introduced in the model parameters using the ETA vector and the additive, proportional or exponential terms as is expressed in **equations 3-1, 3-2 and 3-3** respectively.

PX=TVPX + **ηi** **Equation 3-1**

PX=TVPX + **TVPX** * **ηi** **Equation 3-2**

PX= TVPX * **EXP (ηi)** **Equation 3-3**

Where **PX** represents the individual model parameter value, **TVPX** represents the typical parameter value, and **ηi** represents the difference in the individual parameter **PX** from the typical parameter of population **THETA(x).**

Sometimes an additional level of random effect i.e. intra-individual variability is introduced in the models to account for the inter-occasional variability in the models.

b. Level 2 random effects

The level 2 random effects are introduced as residual unexplained variability parameters accounting to the difference between the observed and predicted concentrations. The error is summed to the predicted concentrations to account for the residual unexplained variability. The error is described by the term εi and the distribution of residual variability is assumed to be normally distributed with mean zero and variance sigma squared.

Random unexplained variability is added using an additive, multiplicative or a combined additive and proportional residual error models as given in **equations 3-4, 3-5 and 3-6** respectively.

Y=IPRED + **ESP(x)** **Equation 3-4**

Y=IPRED + **IPRED** * **EPS(y)** **Equation 3-5**

Y=IPRED + **IPRED** * **EPS(y)** + **EPS(x)** **Equation 3-6**

The term **IPRED** represents the individual predicted concentrations, **EPS(x)** represents the additive part of the residual error while **EPS(y)** represents the proportional part of residual error.

3.1.1.3. Model evaluation and goodness of fit plot

Structural and stochastic parts of nonlinear mixed effect models are evaluated using numerical and graphical goodness of fit plots to determine the agreement between the observed and model-predicted concentrations. The objective function value is usually used to compare the models and helps in decision making regarding the selection of the best model. The difference between the two competing models is χ distributed and a p-value is calculated for a change is objective function by the application of parametric statistics. A model is significantly different from the competing model if there is a drop in the objective function of 3.80 units or more.

Different goodness of fit plots are generated and can help in model diagnostics. The graphs including individually predicted concentrations versus observed plot, population predicted concentration versus observed plots, conditional weighted residuals versus population predicted and time plots give an indication regarding the model selection, performance, and any misspecification.

Epsilon shrinkage value is used to access the level of individual predictions. Epsilon shrinkage is calculated using the expression 100 × (1-σIWRES), where σIWRES expression represents the standard deviation of the individual weighted residual values. When the values of Epsilon shrinkage are less than 20 percent, then the model individual predicted versus observed plots are highly informative.[88]

3.1.1.4. Evaluation of parametric uncertainty

Parametric bootstrap and sampling importance-resampling methods are used to estimate the precision of estimated model parameters by generating many replications of the original datasets and evaluating these data from the final full model. The lower

2.5% or 5% and upper 95.0% or 97.5% value is selected for each parameter to construct the percentile bootstrap confidence intervals.[89]

3.1.1.5. Visual predictive check plots

Visual predictive check plots are used to statistically compare the original observed data and the full final model-based simulated predictions of all individuals at each time point. [90] The main objective of visual predictive check plots is to visually assess if the final model can simulate the central tendency in the observed data and the associated variabilities when it is plotted versus time.[91] Typically 2.5th and 97.5th percentiles of the simulated and observed concentration data are compared.

3.1.1.6. Application of NLME models in the different evaluation of formulations

The validated precise models can be used to evaluate any difference in the pharmacokinetics of drug and metabolite administered and formed from the reference and developed formulation. A covariate analysis can be conducted to evaluate any effect of formulation on the model-estimated parameter. The dichotomous covariate effect can be estimated where an additive, proportional or power shift model can be used to account the absolute or percent difference between the parameters of two formulations as described by the following equation respectively.

P=THETA(X) + **THETA(Y)** * **FORM** **Equation 3-7**

P=THETA(X) * **(1+THETA(Y)** * **FORM)** **Equation 3-8**

P=THETA(X) * **(THETA(Y)** ** **FORM)** **Equation 3-9**

Where **P** represents the model parameter, **THETA(X)** represents the population mean value for reference formulation coded as **FORM=0**, and **THETA(Y)** represents the proportional multiplier for the developed formulation.

Aims and Objectives

The overall aim of the analysis given in Chapter 3 was to build and validate a semi-mechanistic population pharmacokinetic model using non-linear mixed effect modeling approach and to perform a detailed evaluation and comparison of the pharmacokinetics of enalapril and its active metabolite enalaprilat in serum and urine from child-appropriate orodispersible mini-tablets and the reference formulation.

The following four objectives were set to achieve the overall goal,

- To develop a simultaneous semi-mechanistic population pharmacokinetic model of enalapril and enalaprilat in serum and urine using a nonlinear mixed effect modeling.
- To account for any difference in the pharmacokinetics of enalapril and the active metabolite enalaprilat administered and formed from the child-appropriate orodispersible mini-tablet and reference conventional tablets.
- To get deeper insights into the expected pharmacodynamic effect of enalaprilat from the orodispersible mini-tablet and reference conventional difference.
- To account the effect of rapidly dissolved orodispersible formulation on gastric emptying compared to conventional formulation using a population pharmacokinetic modeling approach

3.2. Materials and Method

3.2.1. Trial design and source data of serum and urine concentrations of enalapril and enalaprilat

The dataset for the simultaneous serum and urine population pharmacokinetic modeling analysis consisted of full time versus serum and urine concentration profiles of enalapril and its active metabolite enalaprilat. The dataset consisted of serum and urine concentrations of enalapril and enalaprilat obtained from the phase I clinical trial after the administration of 10mg single extravascular dose of enalapril maleate to 24 healthy subjects in a crossover phase I clinical trial using the reference and developed formulations. Reference treatment consisted of two 5mg strength of enalapril maleate market authorized conventional tablet formulation (Renitec®) administered with 240 ml of water. The developed child-appropriate ODMTs consisted of 10 child-appropriate mini-tablets of 1mg strength administered simultaneously with 240ml of water. Enalapril and enalaprilat serum samples were collected at the time intervals of 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 48 hours after dose administration. Enalapril and enalaprilat urine samples were collected at the time intervals of, 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48 hours after the dose administration. The urine concentrations were converted into the cumulative amount of the drug and metabolite excreted in urine after each time interval. The data sets of drug and metabolite concentrations were merged into a single data set for a simultaneous population pharmacokinetic modeling analysis.

Information related to biometric covariates including age, weight, height, sex and total body water was available to evaluate their relationship with model parameters **Table 3-1.**

The total body water parameter was estimated for male and female subjects by **equation 3-10 and 3-11** respectively.[92]

Total body water for male subjects was approximated by using **equation 3-10**;

$$\textbf{Total body water Vd(L)} = \mathbf{0.3625} * \textbf{Body Weight (kg)} + \mathbf{0.2239} * \textbf{Height}$$

$(\mathbf{cm}) - \mathbf{0.1387} * \mathbf{Age}\ (\mathbf{yr}) - \mathbf{14.47}$ **Equation 3-10**

Total body water for female subjects was calculated by using **equation 3-11**;

$$\mathbf{Total\ body\ water}\ \mathrm{Vd}\ (\mathbf{L}) = 0.2363 * \mathrm{Body\ Weight}\ (\mathrm{kg}) + 0.1962 * \mathrm{Height}\ (\mathrm{cm}) - 0.0272 * \mathrm{Age}\ (\mathrm{yr}) - 10.26$$ **Equation 3-11**

Table 3-1 Summary of biometric covariate values used in population pharmacokinetic analysis.

Biometric covariate	Mean	Median	Minimum	Maximum
AGE (yrs)	28.00	24.40	22.08	47.16
Weight (kg)	69.76	67.60	51.80	95.60
Height (cm)	174.5	176.0	153.0	189.0
Total body water (L)	42.06	41.31	32.86	53.70

3.2.2. Bioanalysis of serum and urine samples for the detection of enalapril and enalaprilat concentrations

Serum and urine concentrations of enalapril and enalaprilat were measured using methods validated according to EMA and FDA guidelines through liquid chromatography triple quadrupole tandem mass spectrometry. The details of the bioanalytical method have been published in the literature.[81]

3.2.3. Population pharmacokinetic modeling

3.2.3.1. Strategy to conduct population pharmacokinetic modeling analysis

1) A simultaneous semi-mechanistic population pharmacokinetic model was developed to predict the pooled data of serum and urine concentrations of enalapril and its active

metabolite enalaprilat representing the ODMTs and the reference formulations. Covariate analysis was conducted to test the effect of formulation on estimated model parameters.

2) In addition to this, the data of ODMT and reference formulations were modeled separately and the individual model estimated pharmacokinetic parameters were statistically correlated to account any difference in the pharmacokinetics of drug and metabolite from the two formulations.

3.2.3.2. Population pharmacokinetic model structure

The population pharmacokinetic model was developed using a nonlinear mixed effect modeling software NONMEM version 7.4.0 (ICON, Development Solutions, Elliot City, MD, USA)[93]. The ADVAN 6 was used where the system of differential equations was written and each compartment was connected by constants of first-order rate transfer. The one and two-compartment models were tested for enalapril. The one, two and three-compartment models were tested to predict enalaprilat concentrations in the combined model. The selection of the appropriate model was based on visual inspection of the goodness of fit plots [94], successful convergence, acceptable relative standard error values, a significant drop in the objective function value and no boundary problems. The maximum likelihood approach using first-order conditional estimation with interaction (FOCE+I) was used for parameter estimation.

After the analysis of goodness of fit plots, objective function value, and the estimated relative standard errors, the one-compartment model disposition parameters were selected for the population pharmacokinetic modeling of enalapril. Previous studies have reported that around 60 % of the total administered enalapril is absorbed from the gastrointestinal tract.[95,96] Therefore, the bioavailability (F1) parameter was estimated to account for the total amount of drug absorbed in central circulation. As per our current knowledge in the literature,[96] it was assumed that enalapril and enalaprilat are only eliminated through urine and the drug is only metabolized to enalaprilat, which is not further metabolized. The assumption is supported by the reported value of the total

amount of dose recovered in urine as enalapril and enalaprilat, which is equal to the total amount of drug absorbed from the gastrointestinal tract.[97] As serum and urine data for the drug and metabolite was available, the system becomes quantifiable and the F1 parameter becomes identifiable and was estimated in the model. The estimated value of the F1 parameter was 60 % and was in line to already published value of 60% of drug absorption given in the literature.[95,96] To predict the lower concentrations at the delayed absorption phase of enalapril, a lag time model and system of transit compartments were used and analyzed.[98] Transit compartments were added in a stepwise approach using the Erlang distribution method where the optimum number of transit compartments were estimated by adding one transit at a time until there was no further drop in the objective function value of 3.8 or more was observed.[88,99] The mean transit time parameter (MTT1) was estimated and rate transfer through transit compartments was calculated using the expression MTT1 = N+1/KTR, where N is the optimal number of transit compartments and KTR is the rate transfer through these transits.[99] The rate constant of absorption (KA) was the transfer rate of the drug from the last transit into the enalapril central compartment. To account for the renal and metabolic elimination pathways, the elimination of enalapril from serum was estimated using rate constants of enalapril elimination through urine (KREN) and eliminated through enalaprilat formation (KM). The volume of distribution of enalapril in the central circulation (VC) and highly perfused tissues was estimated.

The two-compartment model parameters estimated for the modeling of enalaprilat concentrations were rate constant of enalaprilat formation (KM), volume of distribution of enalaprilat in central circulation (VM), rate constants of intercompartmental distribution (KQ1 and KQ2), rate constant of elimination (KME) and mean transit time of enalaprilat formation (MTT2). Transit compartments were added using the Erlang distribution method to predict the lower concentrations enalaprilat formation phase. All the model parameters of enalapril and enalaprilat were identifiable. The blueprints of the combined model are given in **Figure 3-1**.

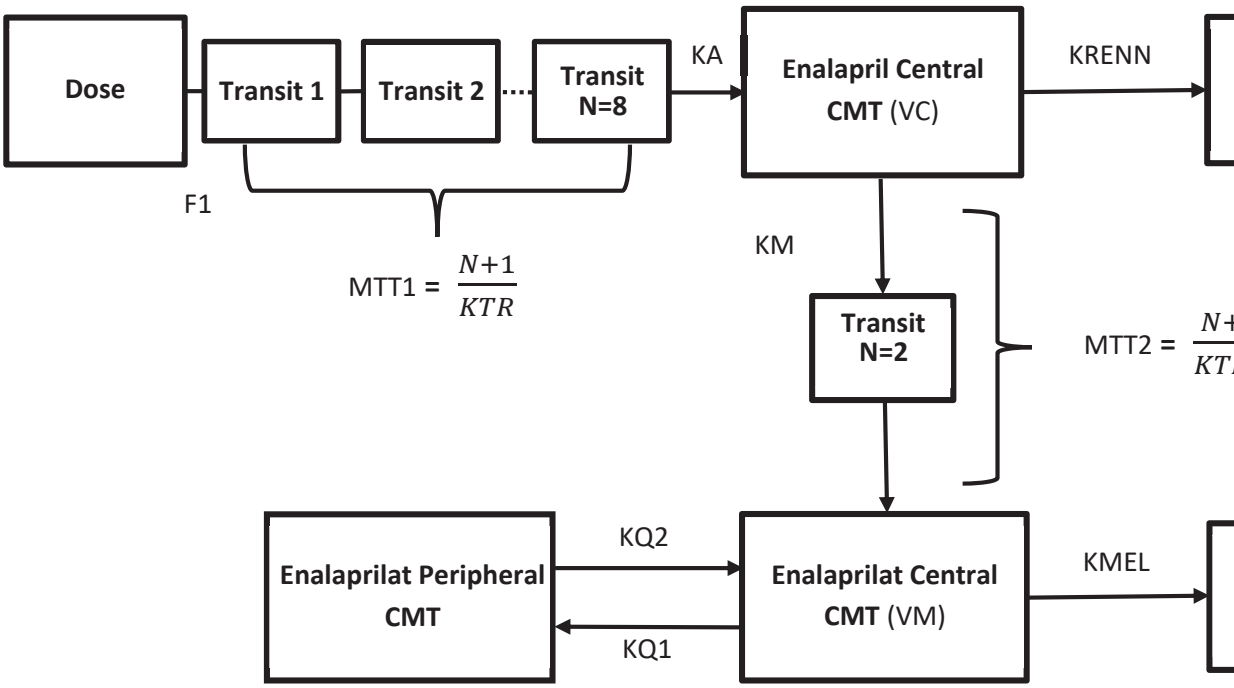


Figure 3-1 Blueprints of the semi-mechanistic population pharmacokinetic model of enalapril and enalapril administration of 10mg of enalapril maleate using reference and ODMT formulations. The system of tra passing through by rate constant (KTR) was used to describe the absorption phase of enalapril, whereas the amount of drug metabolized pre-systemically in the gastrointestinal tract. The parameter (KA) d absorption of the enalapril into the central compartment and instantaneously distribute to highly perfu distribution equals (VC). The biphasic elimination of the drug i.e. bio-transformed to enalaprilat and elimi the parameters (KM) and (KREN) from the central compartment. The formed metabolite transits throug mean residence time (MTT2) into the central compartment and distributing in the central (VM) and to the p and KQ2). The elimination of enalaprilat takes place through the urine compartment (KMEL).

Between-subject variability of parameters was modeled using an exponential error model described as **equation 3-12**.

$$\boldsymbol{Pi = TVpi * \exp(ETA\, i)} \qquad \textbf{Equation 3-12}$$

Where **Pi** was the individual parameter estimate, **TVpi** was the typical mean estimated value of the parameter of the population and **ETAi** was the individual random effect for each parameter per individual. The distribution of ETA in population was assumed to be following a normal distribution with mean zero and variance equals omega square.[100]

Combined additive plus proportional residual error was introduced separately for serum concentrations and separate proportional error was introduced for urine concentrations of enalapril and enalaprilat respectively to account unexplained variability between the observed and predicted concentrations. Residual variability was defined using **equations 3-13 and 3-14**.

$$\boldsymbol{Ci = Cp * (1 + \varepsilon i1) + \varepsilon i2} \qquad \textbf{Equation 3-13}$$

$$\boldsymbol{Ci = Cp * (1 + \varepsilon i1)} \qquad \textbf{Equation 3-14}$$

Where Ci represents the residuals added to the individual concentration, $\mathbf{C_p}$ was the predicted concentrations, **εi** represented the distribution of residuals between enalapril observed and model-predicted concentrations added by both proportional **εi1** and additive terms **εi2**. The distribution of residual variability was assumed to be normally distributed with mean zero and variance sigma squared.

3.2.3.3. Covariate modeling analysis

To build a full population pharmacokinetic model, a stepwise approach was used to evaluate the effect of estimated parameters on biometric covariates. The effect of normalized body weight added on the parameter estimates was evaluated using **equation 3-15**.[101]

$$\boldsymbol{TV = \theta_{TV} * \left(\frac{WT_{ind}}{WT_{ref}}\right)^{\theta}} \qquad \textbf{Equation 3-15}$$

Where **TV** indicates the typical population value of the model estimates, θ_{TV} indicates the typical value of the model estimates for an individual; WT_{ind} indicates body weight of individual subject and WT_{ref} indicates weight normalized by the mean bodyweight of the present study. The parameter **θ** was tested with a fixed value of 1 for the volume of distribution and 0.75 for clearance. The inclusion of covariate was subjected to a significant drop in the objective function of more than 3.8.

For the pooled data analysis, the exponential relationship was incorporated using **equation 3-16** to evaluate the covariate effect of formulation on all model-estimated parameters.

$$TV = \theta X * \theta 12^{FORM} * exp^{\eta} \qquad \textbf{Equation 3-16}$$

Where **TV** represents the typical population value of model parameters, θ_X represents the mean population value of the model parameters, θ_{12} represents a fixed effect parameter to give a proportional increase or decrease in parameter value with ODMT (FORM=1) or reference formulation **(FORM=0)**, and **η** represents inter-individual variability. The full model building process for formulation A, B, and pooled data has been given in **appendix 4 (p. 124).**

3.2.3.4. Population pharmacokinetic model evaluation

The goodness of fit plots were used for the evaluation of model performance. For the evaluation of individual post-hoc estimation with the FOCE+I method of parameter estimation method, conditional weighted residuals were estimated and visual plots given in

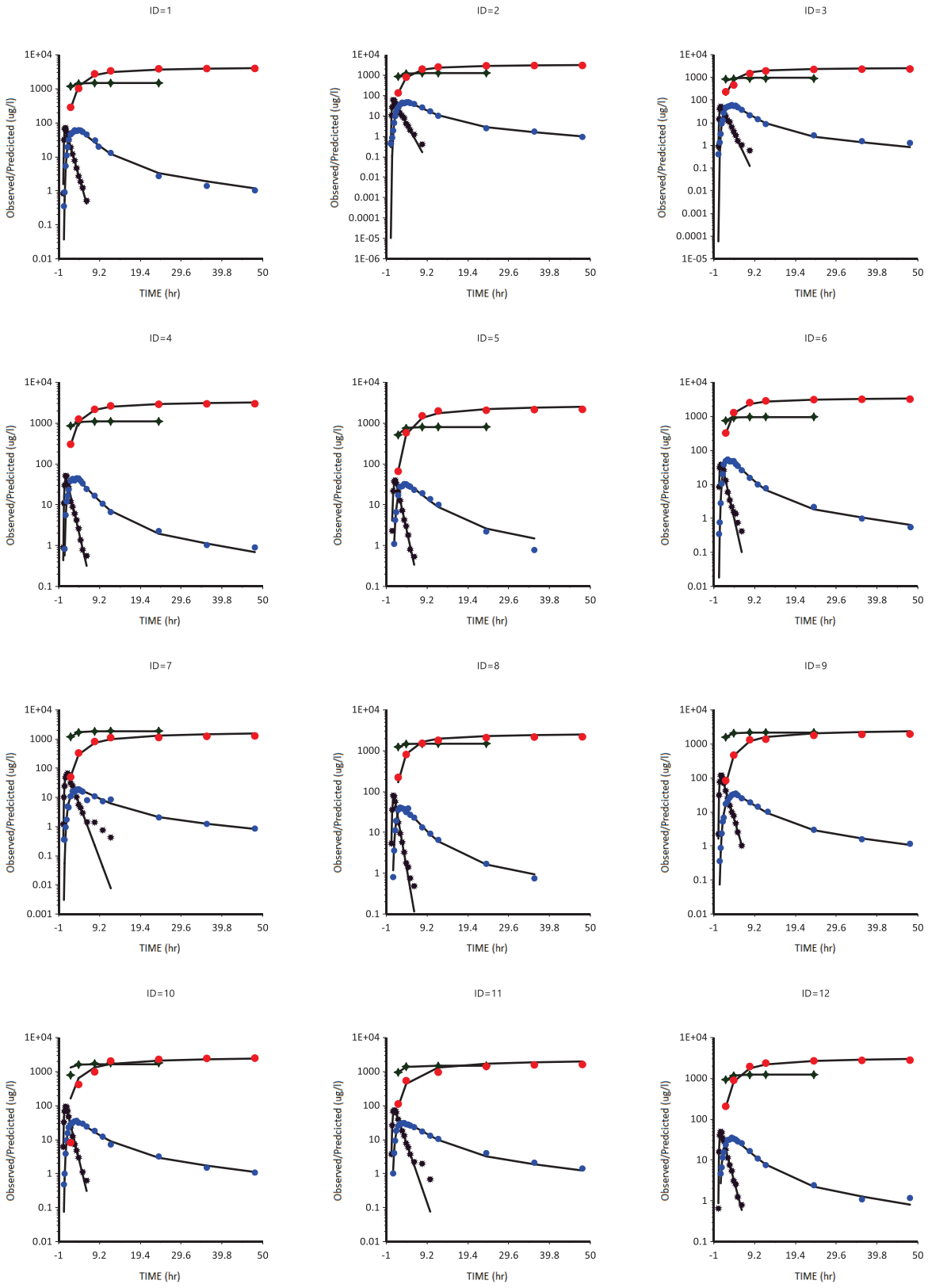
Figure 3-3 were analyzed. The model performance was analyzed from the individual subject predictions of the full profile of enalapril and enalaprilat serum and urine concentration values as given in **Figure 3-2.** Visual predictive check (VPC) plots and the non-parametric bootstrap method was used for model validation. For VPC plots, the final model was used to perform 1000 Monte Carlo simulations.[91] The precision of the estimated model parameters was evaluated using a non-parametric bootstrap method using Perl-speaks-NONMEM (PsN)[102] by calculating the confidence interval (CI) of the

estimated model parameters. The subjects of the original dataset were randomly resampled to create 200 datasets and the new dataset was modeled using the final model. From the bootstrap analysis, the 2.5^{th}, 50^{th} and 97.5^{th} percentiles were simulated. **Table 3-2** summarizes the results of the bootstrap analysis with 95^{th} percent CI values of each parameter.

Due to the long run time of model, a faster than bootstrap method i.e. Sampling importance-resampling (SIR) method was also used to evaluate parameter uncertainty. SIR was performed by running 20,000 final samples and a resample size of 2000. From the SIR method, 95th, CI values were estimated for parameter uncertainty test [103,104]. For the evaluation of the stability of estimated parameters of the model, initial fixed and random effect parameter values were changed stepwise by 10 percent and the population-estimated parameters along with the objective function value were assessed for any change.

3.2.4. Correlation of reference and child-appropriate dosage forms

The covariate effect of formulation on estimated model parameters of the pooled data was assessed using **equation 3-16**. In addition to this, the estimated individual pharmacokinetic parameters of enalapril and enalaprilat of each subject administered ODMTs and reference formulations in two-phase crossover trials were statistically correlated using a paired sample Wilcoxon rank test using an R program with a significant level of $p<0.05$. The rate constants of enalapril and enalaprilat renal elimination were converted to their respective clearance values to correlate the clearances of drug and metabolite following the administration of both formulations.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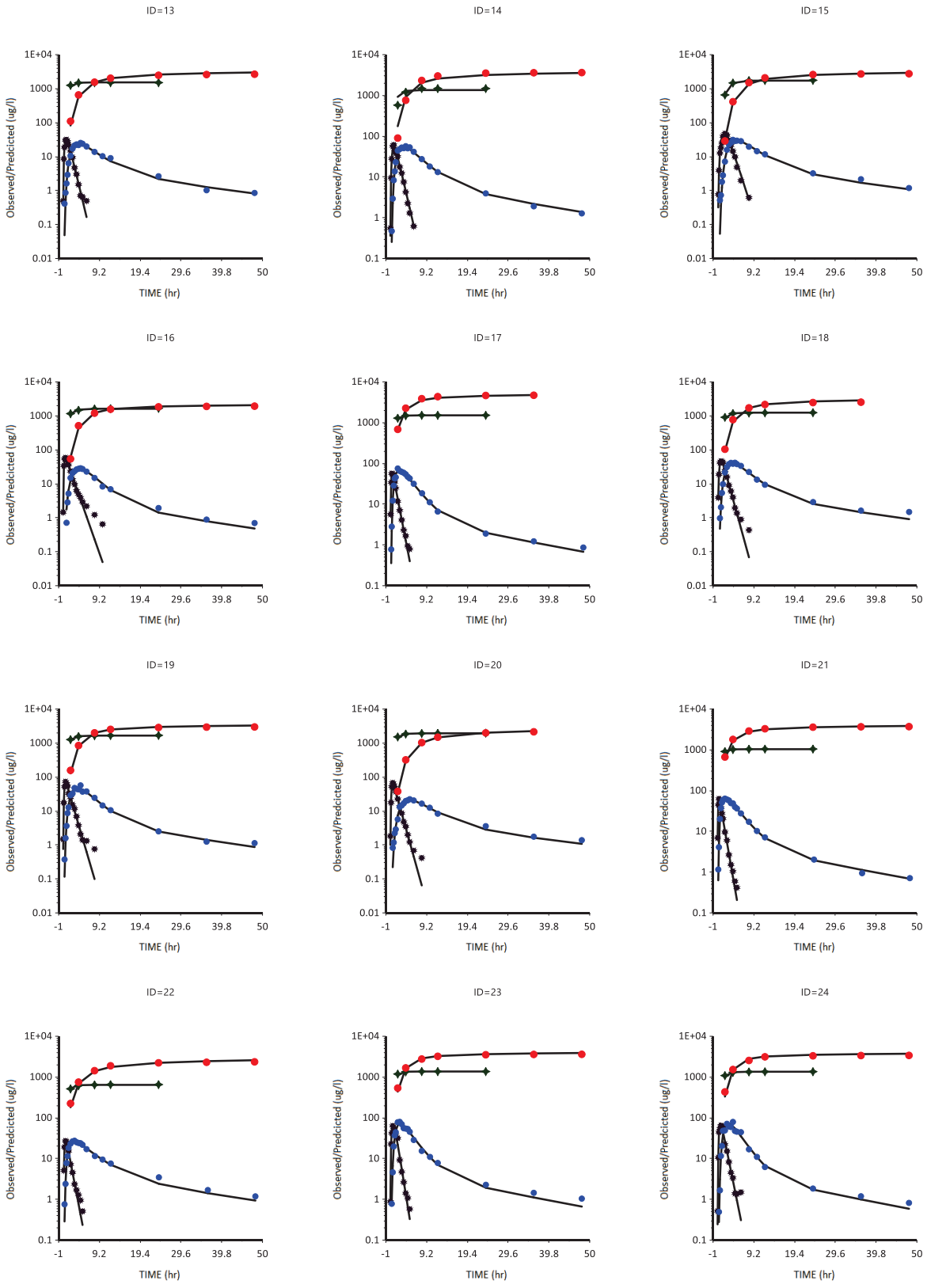
Observed/Predicted (ug/l)
TIME (hr)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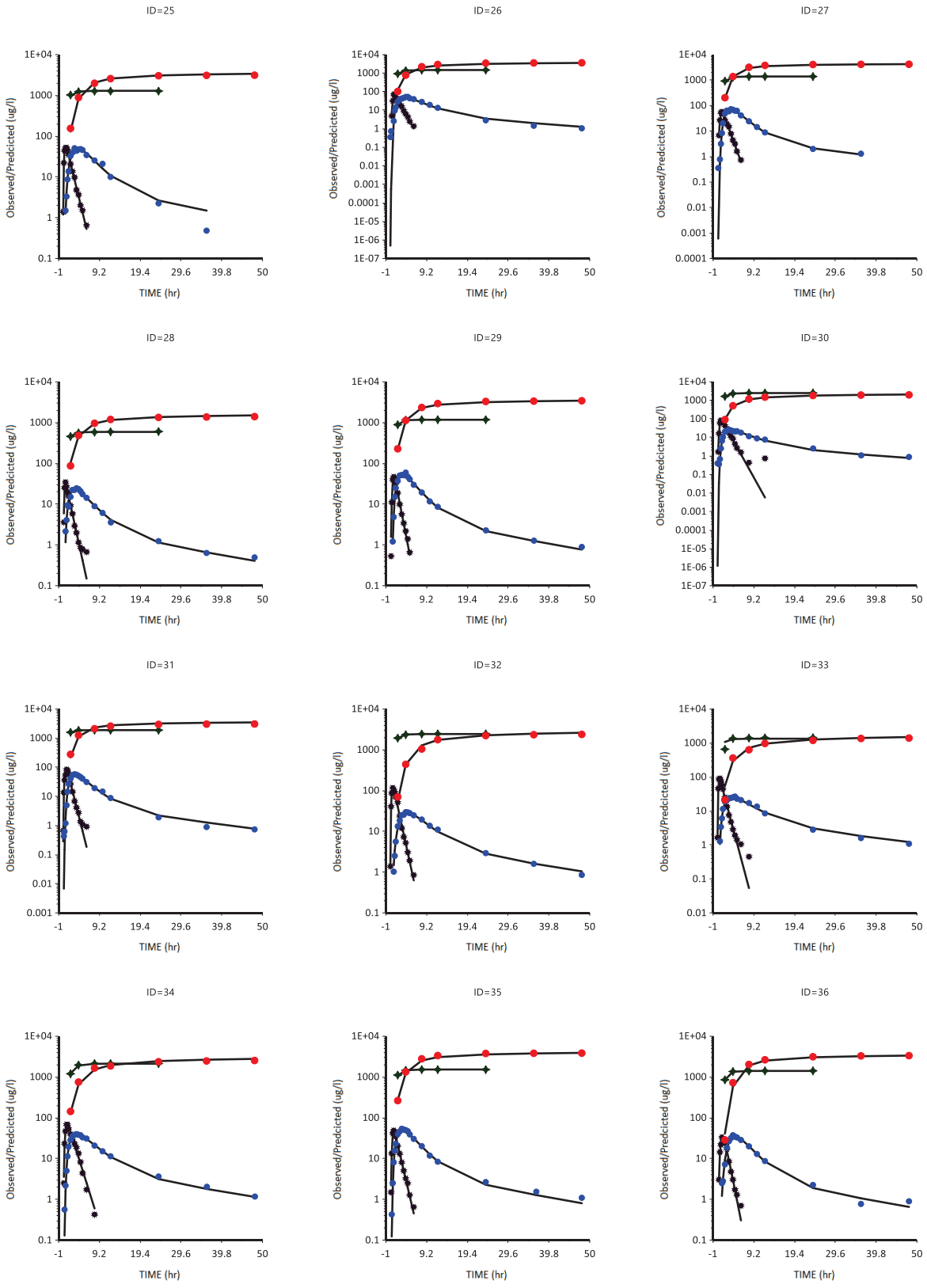
ID=24
Observed/Predicted (ug/l)
TIME (hr)
1E+04
1000
100
10
1
0.1
0.01
-1
9.2
19.4
29.6
39.8
50


ID=25
ID=26
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Observed/Predicted (ug/l)
TIME (hr)

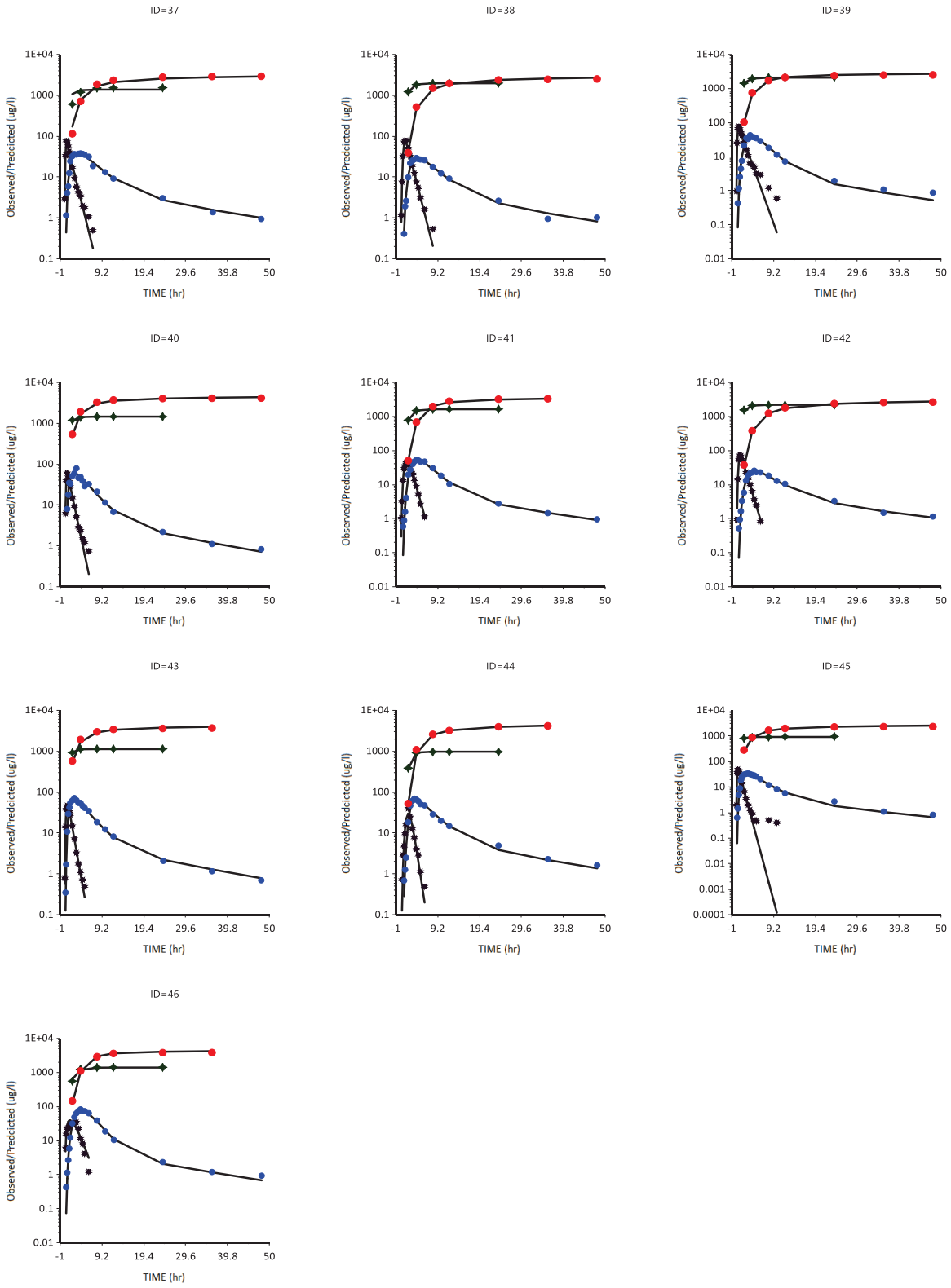


Figure 3-2 Individual time versus observed and model-predicted plots for serum and urine profiles of enalapril and enalaprilat. Green and purple color markers represent serum and urine observed concentrations of enalapril. Blue and red color markers represent serum and urine concentrations of enalaprilat.

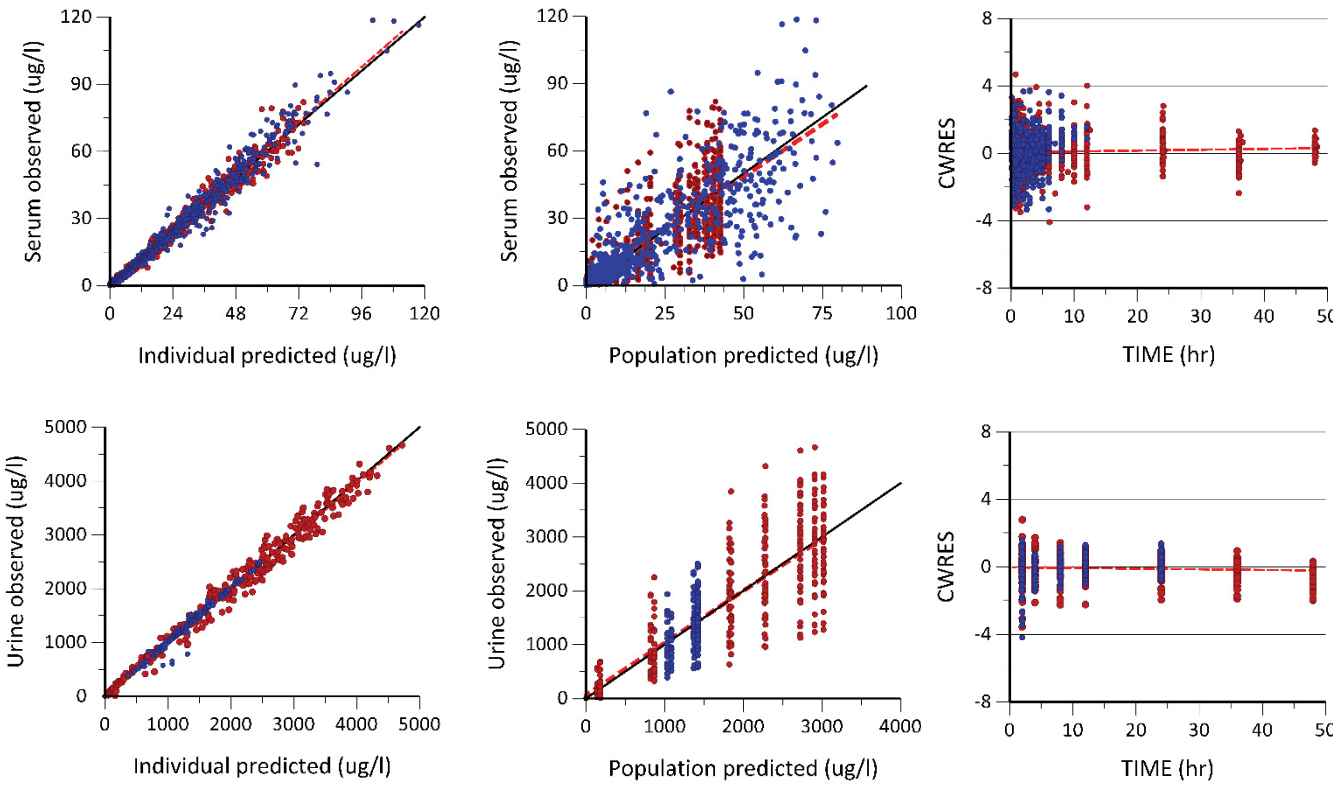


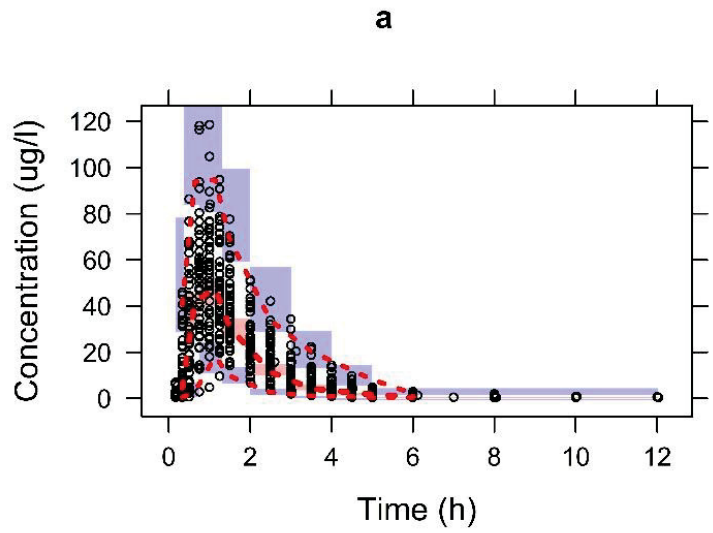
Figure 3-3 Goodness of fit plots including the observed versus individual and population predicted plot (CWRES) versus population predicted (PRED) and time plots of enalapril and enalaprilat in serum and urin pharmacokinetic modeling of pooled data of two formulations. The first row shows the predictive perfor and enalaprilat in serum. The second row shows the predictive performance of enalapril and enalaprilat in represent enalapril concentrations, whereas the red dots represent the enalaprilat concentrations in seru

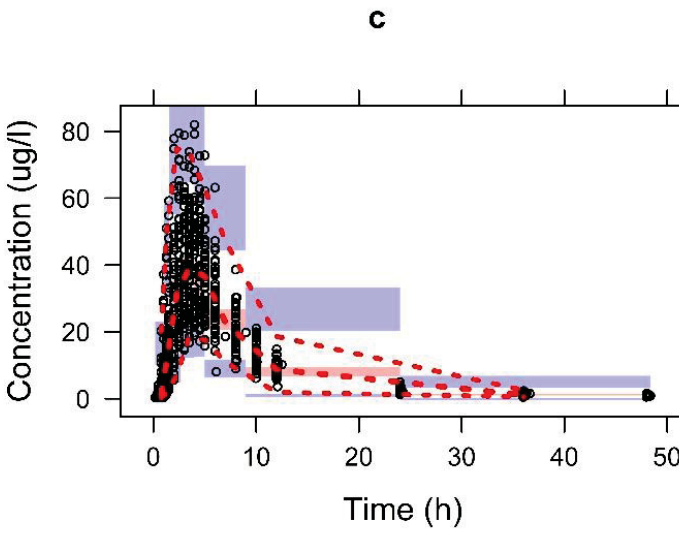
3.3. Results

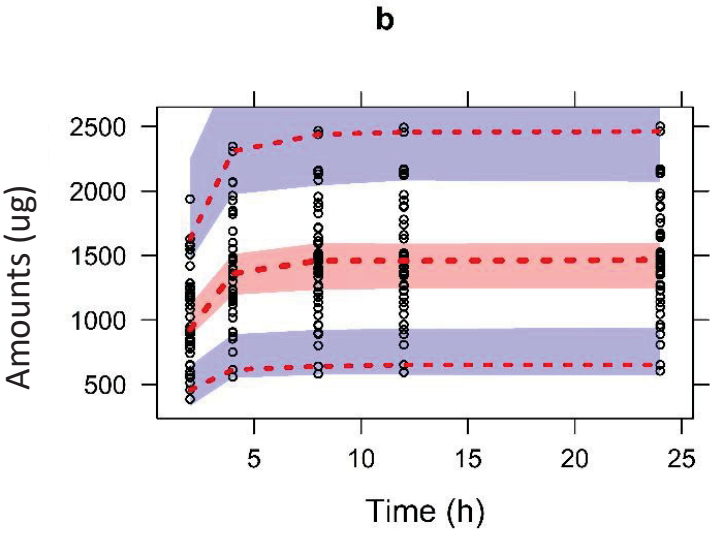
3.3.1. Evaluation of the population pharmacokinetic model

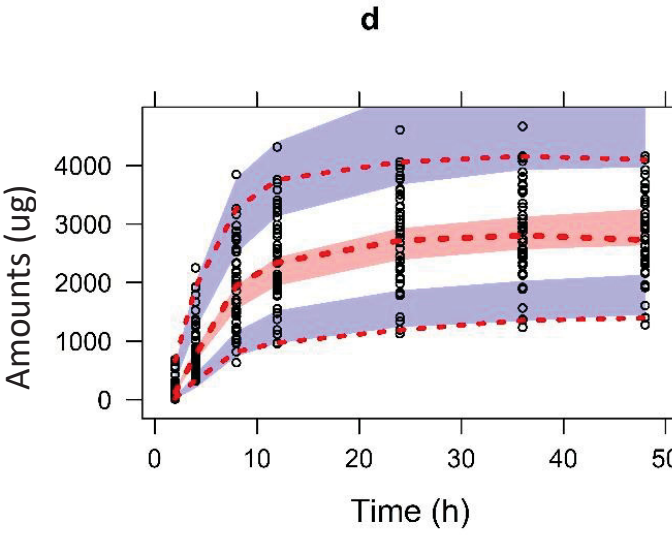
The final population pharmacokinetic model parameter estimates, relative standard errors (RES), SIR and 95th % Bootstrap confidence interval values of the pooled data of the two formulations and of each formulation are given in **Table 3-2, Table 3-4, and Table 3-5** respectively. The RES, SIR and bootstrap confidence intervals for all parameters were narrow and had the same median values as estimated by the model. This shows that parameters were precisely estimated. The goodness of fit plots given in **Figure 3 3, Figure 3 5, and Figure 3 6** shows that the model performed well in predicting the serum and urine concentrations of enalapril and enalaprilat data of treatment A, treatment B, and the pooled data. Eta shrinkage values for most of the parameters were lower than 20 percent and hence the individual model-predicted concentration versus the observed serum and urine concentration plots of enalapril and enalaprilat given in **Figure 3 3, Figure 3 5, and Figure 3 6** was informative and showed agreement between the observed and predicted concentrations.[105] The VPC plots for pooled data analysis given in **Figure 3-4** showed no model misspecification and almost all of the serum and urine observed concentrations were within the prediction intervals.

Visual inspection of the time versus enalapril concentration plot showed a mono-exponential phase of elimination and had no sufficient data for the estimation of the peripheral volume of distribution. The selected one-compartment model adequately predicted the time versus enalapril serum concentrations. The two-compartment model resulted in a significant drop in the objective function but at the expense of higher relative standard errors of the estimated parameters. An optimum number of transit compartments were added using the Erlang distribution method to account for the absorption phase of enalapril. Eight transits (transits=8) were added for reference and pooled data analysis (data of reference + ODMT formulation), and 6 transits were added for the data of ODMT formulation (transits=6). The absorption phase of enalapril was not adequately predicted with or without incorporating a LAG time model.


a
Concentration (ug/l)
Time (h)


c
Concentration (ug/l)
Time (h)


b
Amounts (ug)
Time (h)


d
Amounts (ug)
Time (h)

The introduction of transit compartments resulted in a significant drop in the objective function compared to the lag time model. The bioavailability parameter (F1) accounted for the percent of drug absorbed while subtracting it from the drug eliminated by pre-systemic metabolism. The enalapril population mean parameter estimates along with their relative standard errors are given in **Table 3-2**. The biphasic enalaprilat time vs serum concentration profile was predicted using the two-compartment model. The one-compartment model was not able to predict the second longer phase of elimination.

The two-compartment model also resulted in a significant drop in the objective function value compared to the one-compartment model. A lag time parameter was not able to predict the lower concentrations at the skewed formation phase of enalaprilat; therefore, two-transit compartments were added using the Erlang distribution method to incorporate a delay in metabolite formation. The first-order rate of enalapril and enalaprilat elimination was adequate to predict the cumulative amount of drug and metabolite excreted in the urine. The structure explained in **Figure 3-1** constituted the serum and urine simultaneous semi-mechanistic population pharmacokinetics of enalapril and enalaprilat. Structural population parameters and random variability values have been summarized in **Table 3-2**.

The fixed effect parameters and the random variance were precisely estimated along-with the eta-shrinkage values, lower than 25 %. The forward addition of potential covariate i.e. weight normalized on the volume of distribution of enalapril resulted in a significant drop of the objective function value by 18.2. Similarly, the addition of formulation effect on mean transit time (MTT1) of enalapril further resulted in a significant drop in the objective function by 6.51. The weight normalized on the volume of distribution was tested using the backward elimination method and resulted in a significant increase in the objective function value. Therefore, both covariates were retained in the final population model.

Like the base model, the relative standard error values of the fixed and random effect parameters of the final covariate model showed a precise estimation of the parameters.

Table 3-2 Enalapril and enalaprilat estimated population pharmacokinetic parameters with percent relative standard errors (RES), sampling importance resampling (SIR) and bootstrap confidence interval (CI) values estimated for pooled data analysis.

Parameters	Estimates (% RSE)	Estimates (% RSE)	SIR 95th % CI	Bootstrap 95th % CI
	BASE MODEL	FINAL (FULL) MODEL	FINAL MODEL	FINAL MODEL
Basic pharmacokinetic model parameters				
KA (1/h)	6.060 (14.0 %)	6.010 (15.0 %)	4.780-7.859	4.640-8.200
VC (L)	51.10 (4.00 %)	51.10 (4.00 %)	47.92-54.34	47.38-55.09
F1	0.606 (3.00 %)	0.606 (3.00 %)	0.580-0.640	0.570-0.646
MTT1 (hr)	0.474 (6.00 %)	0.558 (9.00 %)	0.480- 0.640	0.466-0.648
KREN (1/h)	0.305 (4.00 %)	0.305 (4.00 %)	0.290-0.320	0.286-0.330
KM (1/h)	0.688 (4.00 %)	0.688 (4.00 %)	0.640-0.740	0.647-0.725
VM (L)	46.10 (4.00 %)	46.10 (4.00 %)	42.80-49.55	42.21-49.79
KQ1 (1/h)	0.060 (4.00 %)	0.060 (4.00 %)	0.056-0.064	0.056-0.064
KQ2 (1/h)	0.054 (9.00 %)	0.054 (10.0 %)	0.046-0.063	0.048-0.620
KME (1/h)	0.184 (4.00 %)	0.184 (4.00 %)	0.171-0.196	0.171-0.197
MTT2 (h)	0.911 (8.00 %)	0.910 (8.00 %)	0.800-1.044	0.802-1.080
Interindividual variability (IIV)				
IIV_KA	0.683 (30.0 %)	0.688 (31.0 %)	0.474-1.132	0.362-1.005
IIV_VC	0.057 (24.0 %)	0.058 (24.0 %)	0.041-0.086	0.039-0.080
IIV_F1	0.041 (22.0 %)	0.041 (22.0 %)	0.030–0.060	0.023-0.067
IIV_MTT1	0.175 (22.0 %)	0.151 (22.0 %)	0.114-0.220	0.097-0.192
IIV_KREN	0.057 (23.0 %)	0.058 (24.0 %)	0.042-0.084	0.038-0.074
IIV_KM	0.077 (22.0 %)	0.078 (22.0 %)	0.058-0.112	0.050-1.101
IIV_VM	0.068 (24.0 %)	0.069 (23.0 %)	0.050-0.102	0.033-0.105
IIV_KME	0.063 (23.0 %)	0.063 (23.0 %)	0.047-0.092	0.039-0.086
IIV_ MTT2	0.296 (22.0 %)	0.296 (22.0 %)	0.221-0.430	0.196-0.384
Residual unexplained variability (RUV)				
Serum Enalapril				
Proportional error (σ2)	0.010 (8.00 %)	0.010 (8.00 %)	0.008-0.011	0.006-0.013
Additive error (ug/l)	0.188 (15.0 %)	0.188 (15.0 %)	0.150-0.240	0.132-0.294
Serum Enalaprilat				
Proportional error (σ2)	0.018 (9.00 %)	0.018 (9.00 %)	0.015-0.020	0.010-0.026
Additive error (ug/l)	0.224 (13.0 %)	0.220 (13.0 %)	0.180-0.277	0.144-0.301
Urine Enalapril				
Proportional error (σ2)	0.019 (9.00 %)	0.019 (9.00 %)	0.016-0.021	0.009-0.028
Urine Enalaprilat				
Proportional error (σ2)	0.005 (11.0 %)	0.005 (11.0 %)	0.004-0.006	0.002-0.009

The change in the typical population and random variability of the parameters of the base and full covariate models were less than 25 percent and showed that the covariates were clinically unimportant as given in **Table 3-2**.[105]

3.3.2. Pharmacokinetics comparison of ODMT and reference formulation

The pooled data analysis revealed that the formulation had a covariate effect on the mean transit time of enalapril absorption. The results of the paired samples Wilcoxon rank test applied to individual parameters of each formulation modeled separately has been given in **Table 3-3.** The statistical comparison of the parameters also shows a significant difference between the mean transits times of enalapril (MTT1) when the drug was absorbed from ODMT compared to conventional tablets.

Table 3-3 Result of the two-sided paired Wilcoxon rank-sum test to compare pharmacokinetic parameters of enalapril and enalaprilat in serum and urine after the administration of enalapril using ODMT and reference formulation.

P-value	ODMT vs. Reference formulation
KA (1/h)	0.87
VC (L)	0.85
F1	0.19
CLREN (L/h)	0.19
MTT1 (h)	0.033
KM (1/h)	0.70
VM (L)	0.13
MTT2 (h)	0.26
CLENT (L/h)	0.22

The typical population mean value of MTT1 showed that the drug was absorbed around 5 minutes earlier from ODMT compared to the reference formulation. No other pharmacokinetic differences in the comparison of the two formulations were observed. The statistical comparison showed that the two formulations are relatively bioavailable. The pharmacokinetic comparison showed that the drug and metabolite had a similar volume of distribution and clearance from the body.

Table 3-4 Enalapril and enalaprilat estimated population pharmacokinetic parameters with percent relative standard errors (RES), sampling importance resampling (SIR) and bootstrap confidence interval (CI) values estimated for treatment A.

Parameters	Estimates (% RSE)	SIR 95th % CI	Bootstrap 95th % CI
	FINAL (FULL) MODEL	FINAL MODEL	FINAL MODEL
Basic pharmacokinetic model parameters			
KA (1/h)	7.780 (37.0 %)	5.640-11.90	5.541-12.10
VC (L)	51.60 (6.00 %)	46.31-57.06	45.00-55.40
F1	0.630 (5.00 %)	0.574-0.681	0.562-0.667
MTT1 (hr)	0.570 (10.00 %)	0.492-0.681	0.475-0.643
KREN (1/h)	0.312 (5.00 %)	0.281-0.341	0.274-0.339
KM (1/h)	0.683 (7.00 %)	0.605-0.758	0.635-0.746
VM (L)	44.70 (5.00 %)	40.98-48.87	42.10-50.78
KQ1 (1/h)	0.060 (6.0 %)	0.054-0.065	0.053-0.068
KQ2 (1/h)	0.057 (15.0 %)	0.046-0.071	0.045-0.067
KME (1/h)	0.192 (6.00 %)	0.176-0.210	0.175-0.210
MTT2 (h)	0.942 (13.0 %)	0.745-1.144	0.741-1.025
Interindividual variability (IIV)			
IIV_KA	1.310 (53.0 %)	0.796-1.604	0.799-1.522
IIV_VC	0.069 (34.0 %)	0.044-0.120	0.049-0.090
IIV_F1	0.057 (31.0 %)	0.039-0.089	0.041-0.750
IIV_MTT1	0.203 (31.0 %)	0.132-0.338	0.137-0.366
IIV_KREN	0.056 (33.0 %)	0.036-0.097	0.035-0.085
IIV_KM	0.088 (32.0 %)	0.056-0.141	0.050-0.134
IIV_VM	0.048 (35.0 %)	0.029-0.081	0.036-0.102
IIV_KME	0.053 (33.0 %)	0.033-0.088	0.035-0.086
IIV_ MTT2	0.330 (32.0 %)	0.225-0.420	0.243-0.350
Residual unexplained variability (RUV)			
Serum Enalapril			
Proportional error (σ2)	0.010 (12.0 %)	0.007-0.011	0.006-0.014
Additive error (ug/l)	0.189 (21.0 %)	0.137-0.269	0.125-0.245
Serum Enalaprilat			
Proportional error (σ2)	0.021 (14.0 %)	0.016-0.026	0.014-0.026
Additive error (ug/l)	0.220 (22.0 %)	0.159-0.310	0.147-0.316
Urine Enalapril			
Proportional error (σ2)	0.011 (14.0 %)	0.009-0.014	0.007-0.016
Urine Enalaprilat			
Proportional error (σ2)	0.005 (16.0 %)	0.004-0.006	0.003-0.009

Table 3-5 Enalapril and enalaprilat estimated population pharmacokinetic parameters with percent relative standard errors (RES), sampling importance resampling (SIR) and bootstrap confidence interval (CI) values estimated for treatment B.

Parameters	**Estimates (% RES)**	**SIR 95th % CI**	**Bootstrap 95th % CI**
	FINAL (FULL) MODEL	**FINAL MODEL**	**FINAL MODEL**
Basic pharmacokinetic model parameters			
KA (1/h)	7.71 (26.0 %)	5.623-11.59	5.329-12.22
VC (L)	50.70 (5.00 %)	46.87-55.05	47.00-55.59
F1	0.589 (4.00 %)	0.556-0.624	0.553-0.627
MTT1 (hr)	0.484 (7.00 %)	0.438-0.551	0.417-0.553
KREN (1/h)	0.298 (5.00 %)	0.274-0.323	0.274-0.325
KM (1/h)	0.693 (6.00 %)	0.631-0.757	0.641-0.750
VM (L)	47.60 (7.00 %)	42.52-53.20	42.65-52.93
KQ1 (1/h)	0.060 (5.00 %)	0.056-0.066	0.054-0.066
KQ2 (1/h)	0.051 (14.0 %)	0.040-0.064	0.042-0.060
KME (1/h)	0.175 (6.00 %)	0.158-0.193	0.161-0.196
MTT2 (h)	0.873 (11.0 %)	0.732-1.043	0.731-1.015
Interindividual variability (IIV)			
IIV_KA	0.779 (50.0 %)	0.460-1.616	0.215-1.462
IIV_VC	0.047 (34.0 %)	0.031-0.082	0.024-0.070
IIV_F1	0.025 (31.0 %)	0.017–0.042	0.013-0.034
IIV_MTT1	0.269 (30.0 %)	0.184-0.433	0.137-0.366
IIV_KREN	0.056 (31.0 %)	0.037-0.093	0.033-0.076
IIV_KM	0.067 (31.0 %)	0.045-0.111	0.037-0.090
IIV_VM	0.087 (32.0 %)	0.059-0.146	0.042-0.122
IIV_KME	0.071(31.0 %)	0.047-0.117	0.039-0.090
IIV_ MTT2	0.094 (31.0 %)	0.065-0.156	0.043-0.122
Residual unexplained variability (RUV)			
Serum Enalapril			
Proportional error (σ2)	0.010 (12.0 %)	0.008-0.011	0.005-0.014
Additive error (ug/l)	0.186 (23.0 %)	0.133-0.266	0.116-0.425
Serum Enalaprilat			
Proportional error (σ2)	0.016 (13.0 %)	0.013-0.019	0.010-0.024
Additive error (ug/l)	0.220 (17.0 %)	0.170-0.284	0.117-0.316
Urine Enalapril			
Proportional error (σ2)	0.026 (13.0 %)	0.021-0.032	0.011-0.042
Urine Enalaprilat			
Proportional error (σ2)	0.005 (15.0 %)	0.004-0.006	0.001-0.009

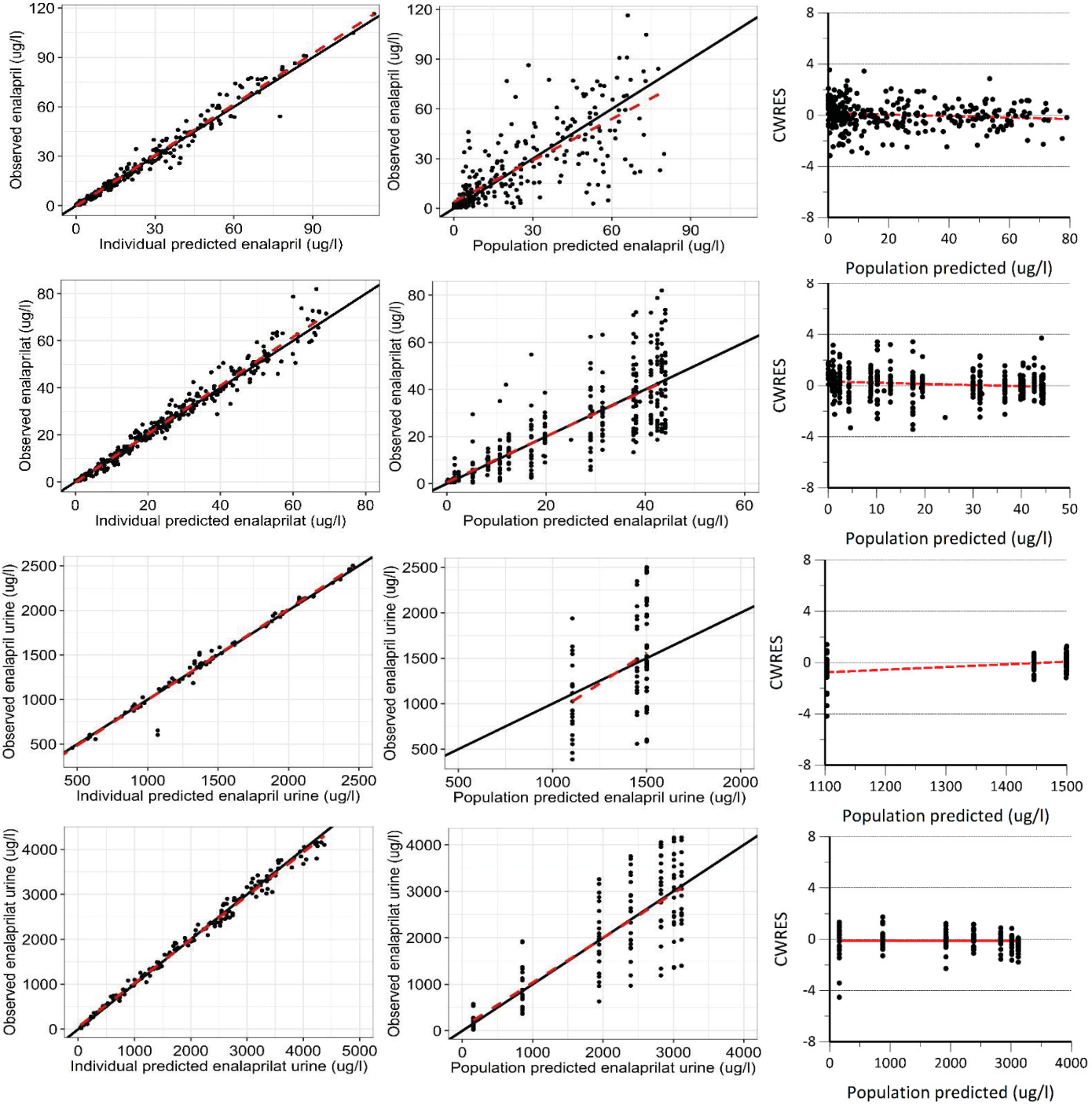


Figure 3-5 Goodness of fit plots including the observed versus individual and population predicted plots, conditional weighted residuals (CWRES) versus population predicted (PRED) and time plots of enalapril and enalaprilat in serum and urine generated after the population pharmacokinetic modeling of **reference tablet formulation**. The first and second row shows the predictive performance of the model for enalapril and enalaprilat in serum. The third and fourth row shows the predictive performance of enalapril and enalaprilat in urine respectively.

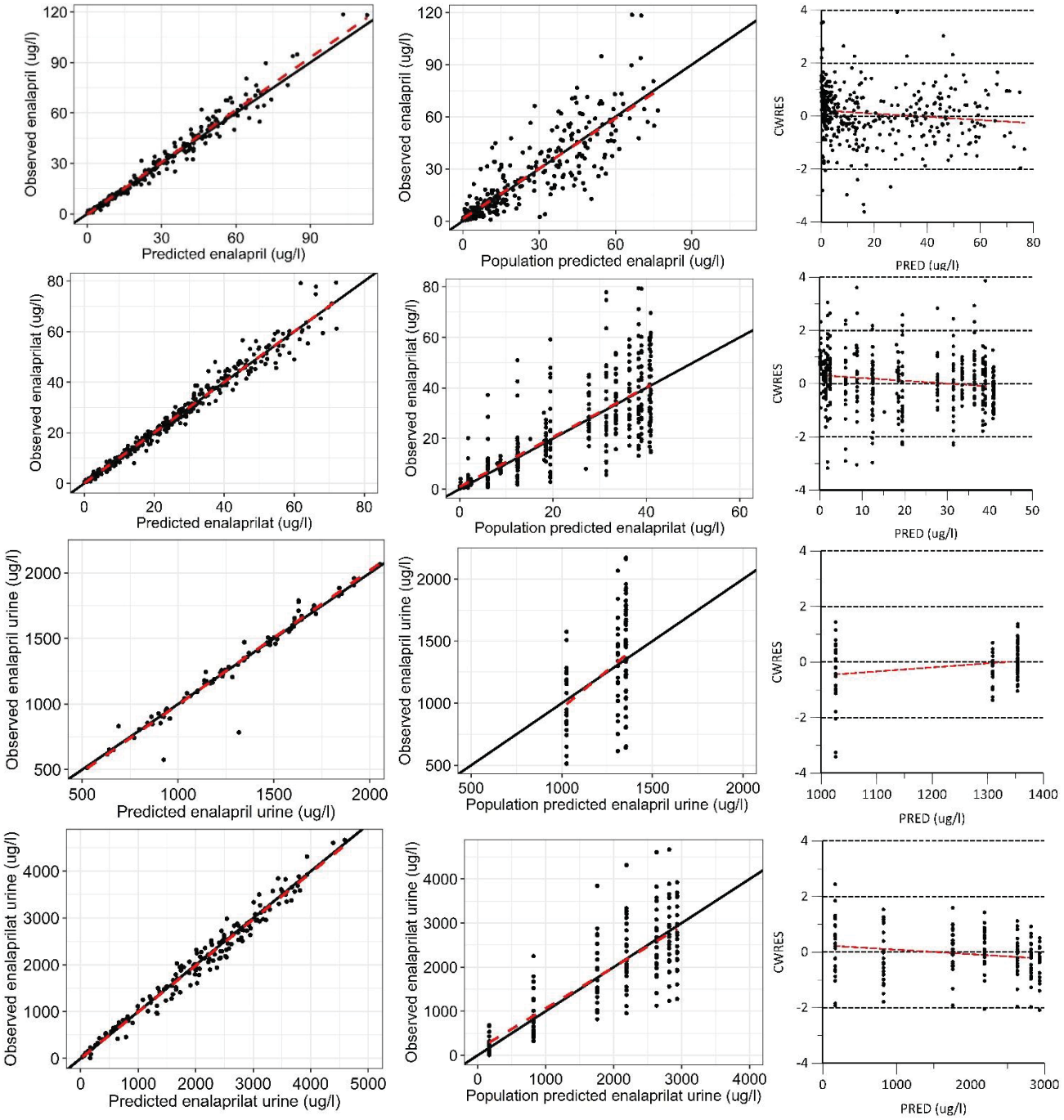


Figure 3-6 Goodness of fit plots including the observed versus individual and population predicted plots, conditional weighted residuals (CWRES) versus population predicted (PRED) and time plots of enalapril and enalaprilat in serum and urine generated after the population pharmacokinetic modeling of **ODMT formulation**. The first and second row shows the predictive performance of the model for enalapril and enalaprilat in serum. The third and fourth row shows the predictive performance of enalapril and enalaprilat in urine respectively.

3.4. Discussion

A nonlinear mixed effect model was developed to get deeper insights relating to the pharmacokinetics of parent drug enalapril and simultaneous formation and disposition of its metabolite enalaprilat from the developed orodispersible mini-tablets and reference formulation. A validated simultaneous semi-mechanistic population pharmacokinetic model adequately predicted the full profiles of serum and urine concentrations of enalapril and enalaprilat. A covariate analysis on population pharmacokinetic model parameters of pooled data showed the effect of formulation on the estimated mean transit time of enalapril absorption from the two formulations. In addition to the pooled data analysis, the statistical comparison of individual pharmacokinetic model parameters estimated separately for ODMTs and reference formulation data revealed that enalapril administered using ODMTs absorbed 5 minutes earlier than the reference tablet formulation. However, no difference in the rate and onset of the formation and disposition of the active ACE-I enalaprilat was noticed. Therefore, no differences in the pharmacodynamics effects are expected from ODMTs compared to the reference formulation.

The selection of the final model was based on the successful convergence with no boundaries, goodness of fit plots, acceptable relative standard errors, and a significant drop in objective function value. Visual predictive check plots,[91] bootstrap analysis,[102] SIR procedure[104] validated the model. The calculated relative standard errors showed that the model parameters were estimated with acceptable precision.

The model informed pharmacokinetic estimates given in **Table 3-2, Table 3-4, and Table 3-5** were in line with the already published value and showed that the population pharmacokinetic model estimated reliable pharmacokinetic parameters. For instance, the estimated fraction of enalapril absorbed was 60 % and was in line with the literature value of 60 %.[95,96] Similarly, the estimated values of the rate constant of absorption and delay in the appearance of enalapril in serum were 6.03 1/h and 0.56 h and were in line with the respective reported value of 6.4 - 12 1/h and 0.5 h.[73] The value of the total rate constant of enalapril elimination through renal and metabolic route was estimated to

be 0.93 1/h and was in line with the reported value of 0.94 1/h.[73] The value of the rate constant of metabolite formation (KM) estimated using a transit compartment model was 0.69 1/h and was in line with the reported value of 0.9 1/h estimated using the LAG time model.[106] The estimated value of the rate constant of enalaprilat elimination was 0.175 1/h and was in line with the reported value of 0.14 1/h.[73]

Semi-mechanistic population pharmacokinetic models have been reported in the literature to predict plasma and urine concentrations of drugs and metabolite.[107] A simultaneous enalapril and enalaprilat population pharmacokinetic model has not been reported in the literature. Based on the goodness of fit plots, objective function, and precision of parameters, the selected one-compartment model was adequate to predict enalapril concentrations and has already been reported in the literature.[19,73] The two-compartment model used for enalapril estimated high standard errors of one or more parameters with no improvement in the goodness of fit plots and therefore was rejected.[100] The one-compartment model using the first order of absorption without accounting a delay in absorption did not account for the absorption phase of enalapril. The LAG time model used to incorporate a delay in absorption did not predict the lower concentrations. A system of transit compartments was used to account for the lower concentrations of the absorption phases of enalapril. The use of transit compartments also resulted in a significant drop in the objective function compared to the LAG time model. The transit compartments were added sequentially as has been used in literature to account for the absorption phase of drugs.[88,108]

The selected two-compartment model for enalaprilat significantly dropped the objective function as compared to the one-compartment model. The one-compartment model was also not able to predict the bi-exponential elimination phase of the metabolite. The two-compartment population pharmacokinetic model with a proportional residual error model has been reported in the literature to model enalaprilat concentrations, however, a combined additive plus proportional residual error model significantly dropped the objective function and was used in our final base model.[106] A three-compartment model

was also tested but resulted in higher standard errors with no significant change in the objective function and was rejected.

The covariate analysis of the pooled data of the two formulations found that formulations have a covariate effect on the mean transit time of enalapril in serum. The pairwise statistical comparison of model parameters estimated separately for ODMT and reference formulation data also showed a difference in mean transit time of enalapril absorption from the two formulations. A comparison of the absolute values of the mean transit time of absorption showed around 5 min early appearance of enalapril in serum from ODMTs compared to the reference formulation. The early appearance of enalapril may be due to the higher surface area of ODMTs provided for fast dissolution and disintegration rates of the developed tablets compared to the reference tablet formulation. The absorption and plasma concentration profile of an orally administered drug also depends on its transit time and absorbability in the gastrointestinal tract. [109] The drug from the small-sized disintegrated and dissolved ODMTs are expected to be emptied earlier from the stomach to reach rapidly at the site of absorption in the intestine. [110] This may lead to the early availability of the drug for absorption. The results are further strengthened by the less number of transit compartments (Transit=6) needed for the enalapril to appear in serum from the ODMTs compared to a higher number of transit compartments (transits=8) for enalapril from the reference formulation to reach in serum. This shows fewer barriers to the drug from ODMTs compared to the reference formulation. Enalapril is a BCS class III drug and follows a permeability-limited absorption from the intestine. Therefore, an early appearance of the drug had no effect on the rate constant of enalapril absorption.

The difference in the model informed transit time of enalapril in the gastrointestinal tract and different excipients of the reference and ODMT formulations had no effect on intestinal permeation i.e. rate constant of absorption of the drug. These results support the bio-waivers given by the FDA to BCS class III drugs whereby the excipients should not have an effect on bioavailability and drug permeability.[111] No other differences in the physiological parameters like the volume of distribution and elimination were

observed for enalapril. The implication of the early appearance of the drug from ODMTs can be useful for classes of drugs like analgesics or in case of an emergency clinical situation such as a hypertensive crisis or an angina attack. For instance, fast disintegrating and dissolving small-sized ODMT formulation of nitroglycerin if developed will require less saliva and can be more beneficial to deliver drug sublingually for achieving early antianginal effect compared to sublingual dosage forms, which require more saliva and higher disintegration time to release the drug.[112] Use of ODMTs may have earlier pharmacodynamics effects, especially for the orally administered BCS class I drugs having higher solubility and permeability. However, in our case, the pro-drug enalapril is inactive and its early appearance will have no expected clinical significance because the pharmacodynamics response will depend on the pharmacokinetics of enalaprilat.

The developed population pharmacokinetic model also informed that the early appearance of drug in the serum had no effect on the onset and rate of enalaprilat biotransformation. This may be due to the same rate constant of absorption and extent of absorption of enalapril from the two formulations. In addition, the uptake of the drug from the systemic circulation into the liver by organic anion-transporting polypeptide (OATP1B1) transporters[113] and the basolateral efflux of the bio-transformed enalaprilat back into the systemic circulation by multidrug resistance-associated protein (MRP4) transporters follows a permeability-limited transport.[114] The volume of distribution and clearance of enalaprilat also showed no difference between the two formulations. Due to similar enalaprilat pharmacokinetics, a similar pharmacodynamics response can be expected from the reference and ODMT formulation.

3.5. Overall summary and conclusion

Acceptability of small-sized orodispersible mini-tablets in pediatrics has been well established.[115] However, the pharmacokinetic comparison was required to assess the efficacy and safety of enalapril administered using the developed orodispersible mini-tablets. Mathematical pharmacokinetic modeling analysis was used to adequately assess the differences in the pharmacokinetics of enalapril administered using the novel orodispersible mini-tablets compared to the reference formulation. The detailed analysis has confirmed an early appearance of enalapril from the orodispersible mini-tablets administered with 240 ml of water compared to the reference formulation.

Both the least square minimization method and the maximum likelihood method of parameter estimation has predicted reliable model parameters. At first, individual pharmacokinetic modeling analysis was performed to predict the enalapril concentrations representing the reference formulation and the developed novel orodispersible mini-tablets. Prior to the pharmacokinetic modeling analysis of the real data set, a simulated validation process was performed to comparing different least-squares minimization methods in order to find and select the most accurate and precise model parameter estimation method. Iteratively reweighted least square minimization method was selected and was used for the individual pharmacokinetic modeling analysis of real datasets. The model parameters obtained from the modeling analysis were used to compare the pharmacokinetics of reference and developed treatments and have revealed that there was a 4 minutes early absorption of enalapril from the orodispersible mini-tablets administered with 240 ml water compared to the reference formulation. No trans-mucosal absorption of enalapril was detected from the orodispersed formulation as the appearance time of the drug from the orodispersible mini-tablets dispersed with 20 ml water and reference formulation was the same. The model-dependent approach was able to inform about the trans-mucosal absorption of drug from the real dataset without conducting expensive and time consuming *in-vitro in-vivo* translational studies.

As enalapril was the prodrug, therefore a simultaneous population pharmacokinetic model was built to model not only the serum and urine concentrations of enalapril but also the serum and urine concentrations of enalaprilat after the administration of enalapril reference and developed formulations. The maximum likelihood method of parameter estimation was used to estimate the model parameters. These parameters were then compared to account any difference in enalaprilat pharmacokinetics from the reference and developed formulations. In addition, a covariate effect of the formulation was evaluated on each model parameter. Similar to the individual modeling analysis, a 5-minute early absorption of enalapril was observed from the novel orodispersible mini-tablets compared to the reference formulation. Absorption phase of enalapril was modeled using transit compartments, whereby 8 transits were added to account the absorption phase of enalapril from reference formulation and 6 transits were used to model the absorption phase of enalapril from the orodispersible mini-tablets. The less number of transit compartments for orodispersible mini-tablets compared to the reference formulation indicated an early gastric emptying of enalapril to be available for early absorption. No other difference in the bioavailability and pharmacokinetics of enalapril, as well as the pharmacokinetics of enalaprilat, was observed in serum and urine after the administration of enalapril from the two formulations. Similar pharmacokinetics of active enalaprilat indicates no expected pharmacodynamics difference from the developed formulation. The overall comparison shows that enalapril and enalaprilat should be safe and effective from the administration of the developed child-appropriate ODMT formulation.

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Appendix 5. Time versus observed and population pharmacokinetic model predicted data for enalapril and enalaprilat in serum and urine.

Appendix 1. R program for the generation of 100 simulated subjects

```
################## ####Simulated data sets for 100 subjects
#######################
########################### Program:
SourceOralW1.R############################
############## Specification of variability and initial values of model
parameters ########
n_subs=100
sub=1:n_subs
VD=100*rlnorm(n_subs,0,0.3)
ke=1*rlnorm(n_subs,0,0.3)
ka=5*rlnorm(n_subs,0,0.3)
tlag=0*rlnorm(n_subs,0,0.003)
dose=100
pk=data.frame(sub,VD,ke,ka,tlag)
write.table(pk,file="B:/100 subjects/Referenz1.csv",sep=",")
################################Specification of Time points
######################
time=c(0.167,0.25,0.5,0.75,1,1.25,1.5,2,3,4,5,6) #12 times sampling total 1200
samples
for (i in 1:n_subs)
{
```

```
if (i==1) subt=cbind(rep(i,12),time)

if (i>1) subt=rbind(subt,cbind(rep(i,12),time))

}

colnames(subt)[1]="sub"

subt=data.frame(subt)

##########################Specification of Bateman

function####################

bat=function(dose,t,VD,ka,ke,tlag){

  dose/VD*ka/(ka-ke)*(exp(-ke*(t-tlag))-exp(-ka*(t-tlag)))

}

pkall=merge(subt,pk,by.subt=sub,by.pk=sub)

pkall$conc=bat(dose,pkall$time,pkall$VD,pkall$ka,pkall$ke,pkall$tlag)

####################Application of 30 percent residual

variability#################

pkall$measured=pkall$conc*(1-rnorm(1200,0,0.3))

pkall$amt=999

pkall=data.frame(pkall)

for(i in (1:1200)){

  if(pkall[i,2]==0)pkall[i,8]=100

}

############################Writing the results as csv

file#######################

write.table(pkall,file="B:/100 subjects/Oral_W1.csv",sep=",")
```

################################Graphical

illustration##############################

```
library(lattice)

ffac=factor(pkall$sub)

xyplot(measured~time|ffac,data=pkall,type="b")
```

Appendix 2. The base model for the population pharmacokinetic modeling analysis of enalapril and enalaprilat in serum and urine.

INDEX 1

; **AUTHOR:** MUHAMMAD FAISAL
; **DATE:** 2/14/19
; **MODEL:** SIMULTANEOUS POP-PK MODEL OF ENALAPRIL AND METABOLITE ENALAPRILAT IN SERUM AND URINE FOR POOLED DATA ANALYSIS

;----------

$PROBLEM SIMULTANEOUS ENALAPRIL ENALAPRILAT POPULATION PHARMACOKINETIC MODEL TO PREDICT RESPECTIVE SERUM AND URINE POOLED CONCENTRATIONS.

;----------

$INPUT ID TIME DV CMT AMT WT HGT SEX AGE BW FORM

;----------

$DATA ALLDATA.csv IGNORE=#-

;----------

$SUBROUTINE ADVAN6 TOL=4

;----------

$MODEL NCOMP=16

```
    COMP=(GUT)                  ;1   ENALAPRIL DEPOT
    COMP=(TRANSIT1)             ;2   ENALAPRIL TRANSIT 1
    COMP=(TRANSIT2)             ;3   ENALAPRIL TRANSIT 2
    COMP=(TRANSIT3)             ;4   ENALAPRIL TRANSIT 3
    COMP=(TRANSIT4)             ;5   ENALAPRIL TRANSIT 4
    COMP=(TRANSIT5)             ;6   ENALAPRIL TRANSIT 5
    COMP=(TRANSIT6)             ;7   ENALAPRIL TRANSIT 6
    COMP=(TRANSIT7)             ;8   ENALAPRIL TRANSIT 7
```

```
COMP=(TRANSIT8)                    ;9   ENALAPRIL TRANSIT 8
COMP=(ENA-CENTRAL)                 ;10 ENALAPRIL CENTRAL
COMP=(ENA-URINE)                   ;11 ENALAPRIL URINE
COMP=(LIVER1)                      ;12 ENALAPRILAT TRANSIT 1
COMP=(LIVER2)                      ;13 ENALAPRILAT TRANSIT 2
COMP=(ENAT-CENTARL)                ;14 ENALAPRILAT CENTRAL
COMP=(ENAT-URINE)                  ;15 ENALAPRILAT URINE
COMP=(ENAT-PERIP)                  ;16 ENALAPRILAT PERIPHERAL
```

$PK

;ENALAPRIL MODEL

```
KA=THETA(1)*EXP(ETA(1)          ENALAPRIL; RATE CONSTANT OF ABSORPTION.
KREN = THETA(2)*EXP(ETA(2))     ENALAPRIL; RATE CONSTANT OF RENAL ELIMINATION.
TVVC = THETA(3)                 ENALAPRIL VOLUME OF DISTRIBUTION IN CENTRAL
                                COMPARTMENT
VC =  TVVC*EXP(ETA(3))
MTT1= THETA(4)) ; ENALAPRIL MEAN TRANSIT TIME OF ABSORPTION.
F1= THETA(5)*EXP(ETA(5))       ;ENALAPRIL FRACTION ABSORBED FROM GIT.
```

;ENALAPRILAT MODEL;

```
KM = THETA(6)*EXP(ETA(6))      ;ENALAPRILAT: RATE CONSTANT OF FORMATION.
Q1=   THETA(7)*EXP(ETA(7)) ;ENALAPRILAT; RATE CONSTANT OF DISTRIBUTION FROM
                            CENTRAL TO PERIPHERAL COMPARTMENT.
Q2=   THETA(8)*EXP(ETA(8)) ;ENALAPRILAT; RATE CONSTANT OF DISTRIBUTION FROM
                            PERIPHERAL TO CENTRAL CMT.
KME= THETA(9)*EXP(ETA(9)) ;ENALAPRILAT; RATE CONSTANT OF RENAL ELIMINATION.
VM =  THETA(10)*EXP(ETA(10)) ;ENALAPRILAT; VOLUME OF DISTRIBUTION   CENTRAL.
MTT2=THETA(11)*EXP(ETA(11); ENALAPRILAT MEAN TRANSIT TIME OF FORMATION.
```

;ENALAPRIL ABSORPTION;

```
KTR1=9/MTT1
```

;ENALAPRILAT ABSORPTION

```
KTR=3/MTT2

;-----------------------------------------------------------------------------------------------

S10=VC
```

```
S14=VM

S15=1

S11=1

;-------------------------------------------------------------------------------------------------
```

$DES ;

```
  DADT(1)=-KTR1*A(1)

  DADT(2)= (F1*KTR1*A(1))-KTR1*A(2)

  DADT(3)= KTR1*A(2)-KTR1*A(3)

  DADT(4)= KTR1*A(3)-KTR1*A(4)

  DADT(5)= KTR1*A(4)-KTR1*A(5)

  DADT(6)= KTR1*A(5)-KTR1*A(6)

  DADT(7)= KTR1*A(6)-KTR1*A(7)

  DADT(8)= KTR1*A(7)-KTR1*A(8)

  DADT(9)= KTR1*A(8)-KA*A(9)

  DADT(10)=KA*A(9)-(KREN+KM)*A(10)

  DADT(11)=KREN*A(10)

  DADT(12)=KM*A(10)-KTR*A(12)

  DADT(13)= KTR*A(12)-KTR*A(13)

  DADT(14)=KTR*A(13)-(Q1+KME)*A(14)+Q2*A(16)

  DADT(15)=KME*A(14)

  DADT(16)=Q1*A(14)-Q2*A(16)

;-------------------------------------------------------------------------------------------------
```

$ ERROR; Compute DV from state variables

```
IF(CMT.EQ.3)IPRED=A(14)/VM

IF(CMT.EQ.2)IPRED=A(10)/VC
```

```
IF(CMT.EQ.5)IPRED=A(15)

IF(CMT.EQ.4)IPRED=A(11)

;-----------------------------------------------------------------------------------------------------

IF(CMT.EQ.3) Y=IPRED*(1+EPS(1))+EPS(2)

IF(CMT.EQ.2) Y=IPRED*(1+EPS(3))+EPS(4)

IF(CMT.EQ.5) Y=IPRED*(1+EPS(5))

IF(CMT.EQ.4) Y=IPRED*(1+EPS(6))

;-----------------------------------------------------------------------------------------------------

$THETA

;-----------------------------------------------------------------------------------------------------

$OMEGA

;-----------------------------------------------------------------------------------------------------

$SIGMA

;-----------------------------------------------------------------------------------------------------

$EST METHOD=1 INTERACTION SIG=3

;-----------------------------------------------------------------------------------------------------

$COV MATRIX=R

;-----------------------------------------------------------------------------------------------------

$TABLE ID TIME CMT DV AMT IPRED RES WRES PRED CWRES KA KM KREN IRES IWRES
Q1 Q2 KME VC VM MTT1 MTT2 F1 NOPRINT ONEHEADER NOAPPEND FILE=mytab.TAB
$TABLE ID TIME IPRED IWRES CWRES IRES IWRES NOPRINT ONEHEADER FILE=sdtab
$TABLE ID KA KM KREN Q1 Q2 KME VC VM MTT1 MTT2 F1 IRES IWRES ETA1 ETA2 ETA3
ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ETA10 ETA11 NOPRINT ONEHEADER FILE=patab
$TABLE ID WT HGT AGE BW NOPRINT ONEHEADER FILE=cotab
$TABLE ID SEX NOPRINT ONEHEADER FILE=cata
```

Appendix 3. The output .lst file generated by NONMEM for the population pharmacokinetic modeling analysis of enalapril and enalaprilat in serum and urine.

Sun 03/24/2019
10:46 PM
;; 1. Based on: run151
;; 2. Description: Combined model with 8/2 transit model and covariate BW/69 and formulation effect on mean transit time
; x1. Author: user
$PROBLEM Combined model with SIX transit for enalapril
$INPUT ID TIME DV CMT AMT WT HGT SEX AGE FORM
$DATA COMBAB.csv IGNORE=#
$SUBROUTINE ADVAN6 TOL=4
$MODEL NCOMP=16 COMP(GUT) COMP(TRANSIT1) COMP(TRANSIT2)
COMP(TRANSIT3) COMP(TRANSIT4) COMP(TRANSIT5)
COMP(TRANSIT6) COMP(TRANSIT7) COMP(TRANSIT8) COMP(CENTRAL)
COMP(URINE) COMP(LIV1) COMP(LIV2) COMP(METACC)
COMP(MURINE) COMP(PERIMETA)
$PK

KA = THETA(1)*EXP(ETA(1)); Rate constant of absorption of enalapril

KM = THETA(2)*EXP(ETA(2)); Rate constant of enalaprilat formation

KREN = THETA(3)*EXP(ETA(3)); Rate constant of enalaril elimination

Q1=THETA(4)*EXP(ETA(4)); Intercompartmental distribution of enalaprilat

Q2=THETA(5)*EXP(ETA(5));Intercompartmental distribution of enalaprilat

KME=THETA(6)*EXP(ETA(6));Rate constant of enalaprilat elimination

TVVC = THETA(7)*WT/69;Volume of distribution of enalapril
VC=TVVC*EXP(ETA(7))

VM = THETA(8)*EXP(ETA(8));Volume of distribution of enalaprilat

MTT1=THETA(9)*EXP(ETA(9)); Mean transit time of enalaprilat absorption

MTT2= THETA(10)*(THETA(12)**FORM)*EXP(ETA(10)); Mean transit time of enalapril absorption

F1 = THETA(11)*EXP(ETA(11)); Fraction of enalapril absorbed

KTR=3/MTT

```
S10=VC
S14=VM
S15=1
S11=1
KTR1=9/AMRT

$DES
 ; Define differential equations
  DADT(1)=-KTR1*A(1)   ; Transit compartments 1 for drug absorption
  DADT(2)= (F1*KTR1*A(1))-KTR1*A(2); Transit compartments 2 for drug absorption
  DADT(3)= KTR1*A(2)-KTR1*A(3); Transit compartments 3 for drug absorption
  DADT(4)= KTR1*A(3)-KTR1*A(4); Transit compartments 4 for drug absorption
  DADT(5)= KTR1*A(4)-KTR1*A(5); Transit compartments 5 for drug absorption
  DADT(6)= KTR1*A(5)-KTR1*A(6); Transit compartments 6 for drug absorption
  DADT(7)= KTR1*A(6)-KTR1*A(7); Transit compartments 7 for drug absorption
  DADT(8)= KTR1*A(7)-KTR1*A(8); Transit compartments 8 for drug absorption
  DADT(9)= KTR1*A(8)-KA*A(9); Transit compartments 9 for drug absorption
  DADT(10)=KA*A(9)-(KREN+KM)*A(10); Central compartment for enalapril
  DADT(11)=KREN*A(10); Renal elimination of enalapril
  DADT(12)=KM*A(10)-KTR*A(12); Metabolic elimination of enalapril
  DADT(13)= KTR*A(12)-KTR*A(13); Delay in enalaprilat formation
  DADT(14)=KTR*A(13)-(Q1+KME)*A(14)+Q2*A(16);  Central compartment for
enalaprilat
  DADT(15)=KME*A(14); Elimination of enalaprilat (Total=renal elimination)
  DADT(16)=Q1*A(14)-Q2*A(16); Peripheral compartment of enalaprilat

$ERROR
 ; Compute DV from state variables
IF(CMT.EQ.3)IPRED=A(14)/VM
IF(CMT.EQ.2)IPRED=A(10)/VC
IF(CMT.EQ.5)IPRED=A(15)
IF(CMT.EQ.4)IPRED=A(11)
IRES=DV-IPRED
W=1/IPRED/IPRED
IWRES=IRES/W
IF(CMT.EQ.3)Y=IPRED*(1+EPS(1))+EPS(2)
IF(CMT.EQ.2)Y=IPRED*(1+EPS(3))+EPS(4)
IF(CMT.EQ.5)Y=IPRED*(1+EPS(5))
IF(CMT.EQ.4)Y=IPRED*(1+EPS(6))

$THETA  (0.00001,5) ; KA
 (0.0000001,0.6) ; KM
 (0.000001,0.2) ; KREN
 (0.0000001,0.06) ; KQ1
 (0.000001,0.06) ; KQ2
```

(0.0000001,0.3) ; KMEL
(0.00001,35.2) ; VC
(0.000001,35.8) ; VM
(0.0000001,0.62) ; MTT
(0.000001,0.16) ; MMTT2
(0.000001,0.518,1) ; BIO
(0,1.05)
$OMEGA
0.81;IIV on KA
0.09;IIV on KM
0.09;IIV on KREN
0 FIX;IIV on Q1
0 FIX;IIV on Q2
0.09;IIV on KMEL
0.09;IIV on VC
0.09;IIV on VM
0.09;IIV on MTT
0.09;IIV on MTT2
0.09;IIV on BIO
$SIGMA
0.16 ; proportional component of enalapril RUV
1 ;Additive component of enalapril RUV
0.16 ;proportional component of enalaprilat RUV
1 ;Additive component of enalaprilat RUV
0.81 ;proportional component of enalapril RUV
0.81 ;proportional component of enalaprilat RUV

$ESTIMATION METHOD=1 INTERACTION SIG=3
$COVARIANCE MATRIX=R

$TABLE ID TIME CMT DV AMT IPRED RES WRES PRED CWRES IRES IWRES KA KM KREN Q1 Q2 KME VC VM MTT AMRT BIO NOPRINT ONEHEADER NOAPPEND FILE=mytab0152.TAB
$TABLE
$TABLE ID ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ETA10 ETA11 NOPRINT ONEHEADER NOAPPEND FILE=0152.ETA
$TABLE ID K12 ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ETA10 ETA11 NOPRINT ONEHEADER FILE=0152.PAR
$TABLE ID TIME WT HGT SEX AGE FORM NOPRINT ONEHEADER FILE=COTAB0152
$TABLE ID TIME SEX NOPRINT ONEHEADER FILE=CATAB0152

NM-TRAN MESSAGES

WARNINGS AND ERRORS (IF ANY) FOR PROBLEM

```
 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.
 (WARNING  3) THERE MAY BE AN ERROR IN THE ABBREVIATED CODE. THE FOLLOWING
 ONE OR MORE RANDOM VARIABLES ARE DEFINED WITH "IF" STATEMENTS THAT DO
NOT
 PROVIDE DEFINITIONS FOR BOTH THE "THEN" AND "ELSE" CASES. IF ALL
 CONDITIONS FAIL, THE VALUES OF THESE VARIABLES WILL BE ZERO.
   IPRED Y
License Registered to Heinrich Heine University
Expiration Date:    14 APR 2019
Current Date:       24 MAR 2019
  **** WARNING!!! Days until the program expires :  20 ****
  **** CONTACT idssoftware@iconplc.com FOR RENEWAL ****
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHINER, AND ALISON BOECKMANN
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
 PERFORMED BY NOUS INFOSYSTEMS
 PROBLEM NO.:         1
0DATA CHECKOUT RUN:              NO
 DATA SET LOCATED ON UNIT NO.:    2
 THIS UNIT TO BE REWOUND:        NO
 NO. OF DATA RECS IN DATA SET:     2123
 NO. OF DATA ITEMS IN DATA SET:  12
 ID DATA ITEM IS DATA ITEM NO.:   1
 DEP VARIABLE IS DATA ITEM NO.:   3
 MDV DATA ITEM IS DATA ITEM NO.: 12
0INDICES PASSED TO SUBROUTINE PRED:
  11   2   5   0   0   0   4   0   0   0   0
0LABELS FOR DATA ITEMS:
 ID TIME DV CMT AMT WT HGT SEX AGE FORM EVID MDV
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
 KA KM KREN Q1 Q2 KME VC VM MTT AMRT BIO IPRED IRES IWRES
0FORMAT FOR DATA:
 (E3.0,E7.0,E12.0,E2.0,2E5.0,E4.0,E2.0,E7.0,E2.0,2F2.0)

 TOT. NO. OF OBS RECS:     2077
 TOT. NO. OF INDIVIDUALS:     46
0LENGTH OF THETA:  12
0DEFAULT THETA BOUNDARY TEST OMITTED:    NO
0OMEGA HAS BLOCK FORM:
  1
  0  2
  0  0  3
  0  0  0  4
  0  0  0  0  5
```

```
 0  0  0  0  0  6
 0  0  0  0  0  0  7
 0  0  0  0  0  0  0  8
 0  0  0  0  0  0  0  0  9
 0  0  0  0  0  0  0  0  0 10
 0  0  0  0  0  0  0  0  0  0 11
0DEFAULT OMEGA BOUNDARY TEST OMITTED:    NO
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION:   6
0DEFAULT SIGMA BOUNDARY TEST OMITTED:    NO
```

INITIAL ESTIMATE OF THETA:

LOWER BOUND	INITIAL EST	UPPER BOUND
0.1000E-04	0.5000E+01	0.1000E+07
0.1000E-06	0.6000E+00	0.1000E+07
0.1000E-05	0.2000E+00	0.1000E+07
0.1000E-06	0.6000E-01	0.1000E+07
0.1000E-05	0.6000E-01	0.1000E+07
0.1000E-06	0.3000E+00	0.1000E+07
0.1000E-04	0.3520E+02	0.1000E+07
0.1000E-05	0.3580E+02	0.1000E+07
0.1000E-06	0.6200E+00	0.1000E+07
0.1000E-05	0.1600E+00	0.1000E+07
0.1000E-05	0.5180E+00	0.1000E+01
0.0000E+00	0.1050E+01	0.1000E+07

INITIAL ESTIMATE OF OMEGA:

BLOCK SET NO.	BLOCK	FIXED
1		NO
	0.8100E+00	
2		NO
	0.9000E-01	
3		NO
	0.9000E-01	
4		YES
	0.0000E+00	
5		YES
	0.0000E+00	
6		NO
	0.9000E-01	
7		NO
	0.9000E-01	
8		NO
	0.9000E-01	
9		NO
	0.9000E-01	
10		NO
	0.9000E-01	

11 NO
0.9000E-01
0INITIAL ESTIMATE OF SIGMA:
0.1600E+00
0.0000E+00 0.1000E+01
0.0000E+00 0.0000E+00 0.1600E+00
0.0000E+00 0.0000E+00 0.0000E+00 0.1000E+01
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.8100E+00
0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.0000E+00 0.8100E+00
0COVARIANCE STEP OMITTED: NO
R MATRIX SUBSTITUTED: YES
S MATRIX SUBSTITUTED: NO
EIGENVLS. PRINTED: NO
COMPRESSED FORMAT: NO
SIGDIGITS ETAHAT (SIGLO): -1
SIGDIGITS GRADIENTS (SIGL): -1
RELATIVE TOLERANCE (TOL): -1
ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY (ATOL): -1
EXCLUDE COV FOR FOCE (NOFCOV): NO
RESUME COV ANALYSIS (RESUME): NO
0TABLES STEP OMITTED: NO
NO. OF TABLES: 1
SEED NUMBER (SEED): 11456
RANMETHOD:
MC SAMPLES (ESEED): 300
WRES SQUARE ROOT TYPE: EIGENVALUE
0-- TABLE 1 --
04 COLUMNS APPENDED: NO
PRINTED: NO
HEADERS: ONE
FILE TO BE FORWARDED: NO
FORMAT: S1PE11.4
LFORMAT:
RFORMAT:
0USER-CHOSEN ITEMS:
ID TIME CMT DV AMT IPRED RES WRES PRED CWRES IRES IWRES KA KM KREN Q1 Q2 KME VC VM MTT AMRT BIO
1DOUBLE PRECISION PREDPP VERSION 7.3.0

GENERAL NONLINEAR KINETICS MODEL (ADVAN6)
0MODEL SUBROUTINE USER-SUPPLIED - ID NO. 9999
0MAXIMUM NO. OF BASIC PK PARAMETERS: 9
0COMPARTMENT ATTRIBUTES
COMPT. NO. FUNCTION INITIAL ON/OFF DOSE DEFAULT DEFAULT
STATUS ALLOWED ALLOWED FOR DOSE FOR OBS.

1	GUT	ON	YES	YES	YES	NO
2	TRANSIT1	ON	YES	YES	NO	NO
3	TRANSIT2	ON	YES	YES	NO	NO
4	TRANSIT3	ON	YES	YES	NO	NO
5	TRANSIT4	ON	YES	YES	NO	NO
6	TRANSIT5	ON	YES	YES	NO	NO
7	TRANSIT6	ON	YES	YES	NO	NO
8	TRANSIT7	ON	YES	YES	NO	NO
9	TRANSIT8	ON	YES	YES	NO	NO
10	CENTRAL	ON	YES	YES	NO	YES
11	URINE	ON	YES	YES	NO	NO
12	LIV1	ON	YES	YES	NO	NO
13	LIV2	ON	YES	YES	NO	NO
14	METACC	ON	YES	YES	NO	NO
15	MURINE	ON	YES	YES	NO	NO
16	PERIMETER	ON	YES	YES	NO	NO
17	OUTPUT	OFF	YES	NO	NO	NO

0NRD VALUE FROM SUBROUTINE TOL: 4

1

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG

COMPT. NO.	**INDICES**				
	SCALE	**BIOAVAIL. FRACTION**	**ZERO-ORDER RATE**	**ZERO-ORDER DURATION**	**ABSORB LAG**
1	*	*	*	*	*
2	*	*	*	*	*
3	*	*	*	*	*
4	*	*	*	*	*
5	*	*	*	*	*
6	*	*	*	*	*
7	*	*	*	*	*
8	*	*	*	*	*
9	*	*	*	*	*
10	10	*	*	*	*
11	13	*	*	*	*
12	*	*	*	*	*
13	*	*	*	*	*
14	11	*	*	*	*
15	12	*	*	*	*
16	*	*	*	*	*
17	*	-	-	-	-

- PARAMETER IS NOT ALLOWED FOR THIS MODEL
* PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
WILL DEFAULT TO ONE IF APPLICABLE

0DATA ITEM INDICES USED BY PRED ARE:
EVENT ID DATA ITEM IS DATA ITEM NO.: 11

```
 TIME DATA ITEM IS DATA ITEM NO.:         2
 DOSE AMOUNT DATA ITEM IS DATA ITEM NO.:   5
 COMPT. NO. DATA ITEM IS DATA ITEM NO.:    4

0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
0ERROR SUBROUTINE INDICATES THAT DERIVATIVES OF COMPARTMENT AMOUNTS
ARE USED.
0DES SUBROUTINE USES COMPACT STORAGE MODE.
1
 #TBLN:      1
 #METH: First Order Conditional Estimation with Interaction
 ESTIMATION STEP OMITTED:              NO
 ANALYSIS TYPE:                     POPULATION
 CONDITIONAL ESTIMATES USED:           YES
 CENTERED ETA:                      NO
 EPS-ETA INTERACTION:                 YES
 LAPLACIAN OBJ. FUNC.:                NO
 NO. OF FUNCT. EVALS. ALLOWED:         3968
 NO. OF SIG. FIGURES REQUIRED:         3
 INTERMEDIATE PRINTOUT:               YES
 ESTIMATE OUTPUT TO MSF:               NO
 IND. OBJ. FUNC. VALUES SORTED:        NO
 NUMERICAL DERIVATIVE
     FILE REQUEST (NUMDER):          NONE
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
 ETA HESSIAN EVALUATION METHOD (ETADER):  0
 INITIAL ETA FOR MAP ESTIMATION (MCETA):  0
 SIGDIGITS FOR MAP ESTIMATION (SIGLO):    100
 GRADIENT SIGDIGITS OF
     FIXED EFFECTS PARAMETERS (SIGL):   100
 EXCLUDE TITLE (NOTITLE):             NO
 EXCLUDE COLUMN LABELS (NOLABEL):       NO
 NOPRIOR SETTING (NOPRIOR):            OFF
 NOCOV SETTING (NOCOV):               OFF
 DERCONT SETTING (DERCONT):            OFF
 ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY(ATOL):-100
 FINAL ETA RE-EVALUATION (FNLETA):       ON
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
     IN SHRINKAGE (ETASTYPE):          NO
 NON-INFL. ETA CORRECTION (NONINFETA):    OFF
 FORMAT FOR ADDITIONAL FILES (FORMAT):    S1PE12.5
 PARAMETER ORDER FOR OUTPUTS (ORDER):     TSOL
 ADDITIONAL CONVERGENCE TEST (CTYPE=4)?:  NO
```

EM OR BAYESIAN METHOD USED: NONE
THE FOLLOWING LABELS ARE EQUIVALENT
PRED=PREDI
RES=RESI
WRES=WRESI
IWRS=IWRESI
IPRD=IPREDI
IRS=IRESI
MONITORING OF SEARCH:
0ITERATION NO.: 0 OBJECTIVE VALUE: 13982.8862351645 NO. OF FUNC. EVALS.: 20
CUMULATIVE NO. OF FUNC. EVALS.: 20
NPARAMETR: 5.0000E+00 6.0000E-01 2.0000E-01 6.0000E-02 6.0000E-02 3.0000E-01 3.5200E+01 3.5800E+01 6.2000E-01 1.6000E-01 5.1800E-01 1.0500E+00 1000E-01 9.0000E-02 9.0000E-02 9.0000E-02 9.0000E-02 9.0000E-02 9.0000E-02 9.0000E-02 9.0000E-02 1.6000E-01 1.0000E+00 1.6000E-01 1.0000E+00 8.1000E-01 8.1000E-01

PARAMETER: 1.0000E-01
GRADIENT: 6.4180E+01 -1.1472E+02 -2.8072E+02 -7.3597E+00 -1.7130E+01 4.3513E+02 -1.6026E+02 -7.9974E+00 -3.5215E+02 -5.9350E+02 1.1780E+02 -2.7210E+02 1.2119E+01 7.0326E-01 -5.9109E+01 -1.4933E+02 -1.3548E+00 2.3773E+01 -1.6562E+02 -4.1847E+02 -1.2213E+01 8.5788E+02 2.8684E+02 4.3941E+02 2.3465E+02 4.6660E+02 1.9955E+02

0ITERATION NO.: 38 OBJECTIVE VALUE: 10275.5354407697 NO. OF FUNC. EVALS.: 36
CUMULATIVE NO. OF FUNC. EVALS.: 1154
NPARAMETR: 6.0135E+00 6.8855E-01 3.0516E-01 6.0242E-02 5.4536E-02 1.8357E-01 5.1058E+01 4.6092E+01 9.1021E-01 5.5790E-01 6.0621E-01 7.3028E-01 6.8835E-01 7.7915E-02 5.7709E-02 6.3050E-02 5.7682E-02 6.8555E-02 2.9578E-01 1.5050E-01 4.1318E-02 9.4606E-03 1.8771E-01 1.7793E-02 2.2226E-01 1.8694E-02 4.9747E-03
PARAMETER: 2.8457E-01 2.3766E-01 5.2252E-01 1.0403E-01 4.5113E-03 -3.9120E-01 4.7192E-01 3.5270E-01 4.8395E-01 1.3490E+00 4.5938E-01 -2.6312E-01 1.8629E-02 2.7907E-02 -1.2219E-01 -7.7942E-02 -1.2243E-01 -3.6089E-02 6.9490E-01 3.5709E-01 -2.8925E-01 -1.3140E+00 -7.3644E-01 -9.9819E-01 -6.5195E-01 -1.7844E+00 -2.4463E+00

GRADIENT: -7.4279E-04 -6.9407E-03 1.5858E-02 -3.5498E-03 5.6450E-03 -3.2380E-02 1.1484E-02 -7.1464E-03 5.0056E-03 -9.4583E-03 -5.6560E-04 9.2029E-04

7.3347E-04 7.6349E-04 3.2595E-03 1.2963E-02 9.2195E-04 -6.0633E-04 -2.3867E-03 -2.4329E-03 1.0759E-03 4.8533E-02 1.6507E-02 -4.1792E-03 -2.5294E-03 1.8990E-02 3.8149E-03

#TERM:
0MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 1154
NO. OF SIG. DIGITS IN FINAL EST.: 3.1

ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

ETABAR: -8.5370E-02 5.0847E-03 4.8038E-03 0.0000E+00 0.0000E+00 9.0755E-04 -5.6499E-03 -1.0061E-03 -1.1310E-04 -1.7499E-02 1.0770E-04

SE: 9.2135E-02 3.9761E-02 3.3551E-02 0.0000E+00 0.0000E+00 3.5752E-02 3.2814E-02 3.6662E-02 7.8710E-02 5.5284E-02
2.9452E-02
N: 46 46 46 46 46 46 46 46 46
46 46

P VAL.: 3.5415E-01 8.9824E-01 8.8615E-01 1.0000E+00 1.0000E+00 9.7975E-01 8.6330E-01 9.7811E-01 9.9885E-01 7.5160E-01 9.9708E-01

ETAshrink(%): 2.3849E+01 2.3225E+00 4.2284E+00 1.0000E+02 1.0000E+02 2.3635E+00 6.3112E+00 3.9820E+00 7.5749E-01 2.2818E+00 6.4469E-01

EBVshrink(%): 2.1153E+01 3.2119E+00 4.7906E+00 0.0000E+00 0.0000E+00 3.3974E+00 6.8785E+00 4.9465E+00 1.6314E+00 3.7530E+00 1.7686E+00

EPSshrink(%): 7.7293E+00 7.7293E+00 1.0803E+01 1.0803E+01 7.8547E+00 1.0888E+01

#TERE:
Elapsed estimation time in seconds: 18359.43
Elapsed covariance time in seconds: 95553
1

****
********FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION ***********
OBJT:*************MINIMUM VALUE OF OBJECTIVE FUNCTION***************
****
****
#OBJV:*********** ******* ****** 10275.535 **************************

****
****
**********FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION********
**********FINAL PARAMETER ESTIMATE **********
****
**********THETA - VECTOR OF FIXED EFFECTS PARAMETERS**********

TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 TH 9 TH10 TH11 TH12
6.01E+00 6.89E-01 3.05E-01 6.02E-02 5.45E-02 1.84E-01 5.11E+01 4.61E+01 9.10E-01 5.58E-01 6.06E-01 7.30E-01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ET10 ET11
ETA1
+ 6.88E-01
ETA2
+ 0.00E+00 7.79E-02
ETA3
+ 0.00E+00 0.00E+00 5.77E-02
ETA4
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00
ETA5
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00
ETA6
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 6.30E-02
ETA7
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 5.77E-02
ETA8
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 6.86E-02
ETA9
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 2.96E-01
ET10
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.51E-01
ET11
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 4.13E-02

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS **

EPS1 EPS2 EPS3 EPS4 EPS5 EPS6
EPS1
+ 9.46E-03

EPS2
+ 0.00E+00 1.88E-01
EPS3
+ 0.00E+00 0.00E+00 1.78E-02
1
EPS1 EPS2 EPS3 EPS4 EPS5 EPS6
EPS4
+ 0.00E+00 0.00E+00 0.00E+00 2.22E-01
EPS5
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.87E-02
EPS6
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 4.97E-03
1
OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ET10
ET11**
ETA1
+ 8.30E-01
ETA2
+ 0.00E+00 2.79E-01
ETA3
+ 0.00E+00 0.00E+00 2.40E-01
ETA4
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00
ETA5
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00
ETA6
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 2.51E-01
ETA7
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 2.40E-01
ETA8
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 2.62E-01
ETA9
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00
5.44E-01
ET10
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00
0.00E+00 3.88E-01
ET11
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00
0.00E+00 0.00E+00 0.00E+00 2.03E-01

SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS *
EPS1 EPS2 EPS3 EPS4 EPS5 EPS6**
EPS1

+ 9.73E-02
EPS2
+ 0.00E+00 4.33E-01
EPS3
+ 0.00E+00 0.00E+00 1.33E-01
EPS4
+ 0.00E+00 0.00E+00 0.00E+00 4.71E-01
EPS5
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.37E-01
EPS6
+ 0.00E+00 0.00E+00 0.00E+00 0.00E+00 0.00E+00 7.05E-02
1
****
**********FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION**********
**********STANDARD ERROR OF ESTIMATE**********
****

THETA - VECTOR OF FIXED EFFECTS PARAMETERS *******
TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 TH 9 TH10 TH11 TH12**
9.10E-01 2.96E-02 1.16E-02 2.26E-03 5.51E-03 7.55E-03 1.99E+00 2.01E+00 7.49E-02 4.78E-02 1.90E-02 8.64E-02
OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ******
ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ET10 ET11**
ETA1
+ 2.12E-01
ETA2
+ 1.74E-02
ETA3
+ 1.31E-02
ETA4
+ ....
ETA5
+ ....
ETA6
+ 1.43E-02
ETA7
+ 1.38E-02
ETA8
+ 1.61E-02
ETA9
+ 6.43E-02
ET10
+ 3.28E-02
ET11

+ 8.97E-03
SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS **
EPS1 EPS2 EPS3 EPS4 EPS5 EPS6
EPS1
+ 7.94E-04
EPS2
+ 2.90E-02
EPS3
+ 1.67E-03
EPS1 EPS2 EPS3 EPS4 EPS5 EPS6
EPS4
+ 2.95E-02
EPS5
+ 1.76E-03
EPS6
+ 5.35E-04
1
OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8 ETA9 ET10
ET11
ETA1
+ 1.28E-01
ETA2
+ 3.11E-02
ETA3
+ 2.72E-02
ETA4
+ ....
ETA5
+ ....
ETA6
+ 2.85E-02
ETA7
+ 2.87E-02
ETA8
+ 3.08E-02
ETA9
+ 5.91E-02
ET10
+ 4.23E-02
ET11
+ 2.21E-02
SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS *
EPS1 EPS2 EPS3 EPS4 EPS5 EPS6
EPS1

+ 4.08E-03
EPS2
+ 3.34E-02
EPS3
+ 6.25E-03
EPS4
+ 3.13E-02
EPS5
+ 6.42E-03
EPS6
+ .... 3.79E-03.

Appendix 4. Population pharmacokinetic model development by incorporating transit compartments and covariates for formulation A, B, and the pooled data sets.

Table Appendix 4-1 Population pharmacokinetic model development of enalapril and enalaprilat in serum and urine representing formulation A. Bold model represents the final model.

Run. No	Ref. No	Formulation A		
		Model development	**OBJ FNC**	**Δ OBJ FNC**
Run.1		Enalapril =1 Transit / Enalaprilat =1 Transit	5698.42	95.844
Run.2	**Run.1**	Enalapril =2 Transit / Enalaprilat =1 Transit	5489.18	-209.24
Run.3	**Run.2**	Enalapril =3 Transit / Enalaprilat =1 Transit	5331.18	-158.00
Run.4	**Run.3**	Enalapril =4 Transit / Enalaprilat =1 Transit	5218.97	-112.21
Run.5	**Run.4**	Enalapril =5 Transit / Enalaprilat =1 Transit	5139.60	-79.36
Run.6	**Run.5**	Enalapril =6 Transit / Enalaprilat =1 Transit	5092.61	-46.98
Run.7	**Run.6**	Enalapril =7 Transit / Enalaprilat =1 Transit	5064.86	-27.75
Run.8	**Run.7**	**Enalapril =8 Transit / Enalaprilat =1 Transit**	**5047.33**	**-4.546**
Run.9	**Run.8**	Enalapril =9 Transit / Enalaprilat =1 Transit	5048.84	+1.510
Run.10	**Run.8**	**Enalapril =8 Transit / Enalaprilat =2 Transit Final base model**	**4909.30**	**-138.03**
Run.11	**Run.10**	Enalapril =8 Transit / Enalaprilat =3 Transit	4921.50	+12.2
Run.8	**Run.10**	**Final base model + BW/69**	**4903.95**	**-5.350**

Table Appendix-4-2 Population pharmacokinetic model development of enalapril and enalaprilat in serum and urine representing formulation B. Bold model represents the final model.

Run. No	Ref. No	Formulation B		
		Model development	**OBJ FNC**	**Δ OBJ FNC**
Run.1		LAG TIME Model	5823.75	
Run.2	**Run.1**	Enalapril =1 Transit / Enalaprilat =1 Transit	6017.47	+193.71
Run.3	**Run.2**	Enalapril =2 Transit / Enalaprilat =1 Transit	5789.87	-227.59
Run.4	**Run.3**	Enalapril =3 Transit / Enalaprilat =1 Transit	5617.18	-172.68
Run.5	**Run.4**	Enalapril =4 Transit / Enalaprilat =1 Transit	5510.41	-106.76
Run.6	**Run.5**	Enalapril =5 Transit / Enalaprilat =1 Transit	5461.38	-49.03
Run.7	**Run.6**	Enalapril =6 Transit / Enalaprilat =1 Transit	5442.26	-19.12
Run.8	**Run.7**	Enalapril =7 Transit / Enalaprilat =1 Transit	5440.629	-1.635
Run.9	**Run.7**	**Enalapril =6 Transit / Enalaprilat =2 Transit final base model**	**5346.27**	**-95.99**
Run.10	**Run.9**	Enalapril =6 Transit / Enalaprilat =3 Transit	5388.79	+42.52
Run.11	**Run.9**	**Final base model +BW/69**	**5333.01**	**-13.26**

Table Appendix-4-3 Population pharmacokinetic model development of enalapril and enalaprilat in serum and urine representing the pooled data of formulation A and B. Bold model represents the final model.

Run. No	**Ref. No**	**Pooled data of formulation A and B**		
		Model development	**OBJ FNC**	**Δ OBJ FNC**
Run.1		Enalapril =5 Transit/Enalaprilat =2 Transit	10420.48	
Run.2	**Run.1**	Enalapril =6 Transit/Enalaprilat =2 Transit	10336.504	-84.0
Run.3	**Run.2**	Enalapril =7 Transit/Enalaprilat =2 Transit	10317.28	-19.2
Run.4	**Run.3**	**Enalapril =8 Transit/Enalaprilat =2 Transit**	**10300.32**	**-7.12**
Run.5	**Run.4**	Enalapril =9 Transit/Enalaprilat =2 Transit	10300.42	-0.10
Run.6	**Run.4**	**Enalapril =8 Transit/Enalaprilat =2 Transit BW/69**	**10282.158**	**-18.162**
Run.7	**Run.6**	**Enalapril =8 Transit/Enalaprilat =2 Transit/BW/69 + AMRT**	**10275.535**	**-6.6**
Run.8	**Run.7**	**Enalapril =8 Transit/Enalaprilat =2 Transit /AMRT Backward elimination**	**10293.72**	**-18.19**
Run.9	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on KA	10281.97	-0.188
Run.10	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on KM	10282.15	-0.008
Run.11	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on KREN	10281.64	-0.518
Run.12	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on KMEL	10281.53	-0.628
Run.13	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on VM	10281.89	-0.268
Run.14	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on MTT1	10282.06	+0.098
Run.15	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on VC	10295.05	+12.89
Run.16	**Run.7**	Enalapril =8 Transit/Enalaprilat =2 Transit, covariate=BW/69 + Formulation effect on BIO	10280.87	-1.288

Appendix 5. Time versus observed and population pharmacokinetic model predicted data for enalapril and enalaprilat in serum and urine.

ID	TIME	CMT	DV	AMT	IPRED	PRED	CWRES
1	0	1	0	7640	0	0	0
1	0.167	2	0.838	0	1.5662	0.33259	-1.5632
1	0.333	3	0.354	0	0.03724	0.01098	0.73363
1	0.333	2	31.4	0	30.297	10.331	0.4084
1	0.5	3	0.908	0	0.53819	0.20158	0.89374
1	0.5	2	66.2	0	62.329	31.531	0.66792
1	0.75	3	5.36	0	4.0288	1.933	2.5704
1	0.75	2	71	0	63.514	45.877	0.65733
1	1	3	10.94	0	11.508	6.4154	-0.01981
1	1	2	54.2	0	51.067	41.991	0.16784
1	1.25	3	19.32	0	21.395	13.034	-0.54106
1	1.25	2	40.8	0	40.221	34.191	-0.12522
1	1.5	2	30.6	0	31.639	26.991	-0.40968
1	1.5	3	31.8	0	31.68	20.334	0.40213
1	2	2	18.96	0	19.576	16.494	-0.28339
1	2	3	45.2	0	48.601	32.746	-0.47013
1	2	5	283.31	0	261.45	179.8	0.76899
1	2	4	1173.1	0	1148.5	1084.8	0.11561
1	2.5	2	11.96	0	12.112	10.039	-0.06466
1	2.5	3	51.6	0	58.352	39.952	-0.99567
1	3	2	7.76	0	7.4937	6.1084	0.30753
1	3	3	60	0	61.967	42.63	-0.15905
1	3.5	2	4.64	0	4.6364	3.7166	0.084692
1	3.5	3	57	0	61.494	42.354	-0.59728
1	4	2	2.68	0	2.8686	2.2613	-0.23273
1	4	3	60.2	0	58.645	40.405	0.40838
1	4	5	1011.2	0	1186.6	867.44	-1.0626
1	4	4	1404	0	1418.7	1376	-0.26893
1	4.5	2	1.852	0	1.7749	1.3759	0.21483
1	4.5	3	59.2	0	54.588	37.627	0.98135
1	5	2	1.226	0	1.0981	0.83714	0.31543
1	5	3	53.8	0	50.051	34.529	0.8555
1	6	2	0.514	0	0.42037	0.30991	0.23013
1	6	3	45.2	0	41.054	28.408	1.0505
1	8	4	1466.9	0	1464.1	1421.4	-0.01604
1	8	5	2726	0	2490.4	1844.5	0.88862
1	8.117	3	30.2	0	26.136	18.272	1.4223
1	9	3	19.78	0	21.709	15.252	-1.112
1	12	3	13	0	12.169	8.6856	0.31418

1	12	4	1466.9	0	1465.1	1422.3	-0.02111
1	12	5	3335.6	0	3062.4	2281.5	0.955
1	24	3	2.7	0	3.309	2.4031	-1.3414
1	24	4	1466.9	0	1465.1	1422.3	-0.02116
1	24	5	3825.3	0	3629.2	2724.9	0.79473
1	36	3	1.392	0	1.8953	1.3776	-1.1991
1	36	5	3887.6	0	3862.8	2908.6	0.48003
1	48	5	3922.4	0	4004.1	3020.1	0.30337
1	48.017	3	1.032	0	1.1784	0.86103	-0.41584
2	0	1	0	7640	0	0	0
2	0.167	3	0.43	0	1.06E-05	2.39E-05	0.99248
2	0.167	2	0.486	0	0.29681	0.4677	0.44752
2	0.333	2	10.62	0	10.322	14.528	0.95789
2	0.5	3	0.856	0	0.11023	0.20158	1.7354
2	0.5	2	26.6	0	34.089	44.34	-1.1169
2	0.75	3	1.912	0	1.188	1.933	1.7223
2	0.75	2	61	0	52.859	64.514	0.81454
2	1	3	4.56	0	4.3379	6.4154	0.60862
2	1	2	57.8	0	50.141	59.049	0.43712
2	1.25	3	9.66	0	9.5611	13.034	0.36918
2	1.25	2	43	0	42.288	48.081	-0.58607
2	1.5	3	16.3	0	16.016	20.334	0.38281
2	1.5	2	34.4	0	34.721	37.956	-0.6533
2	2	2	20.2	0	23.093	23.195	-1.2035
2	2	3	26.4	0	29.01	32.746	-0.86545
2	2	5	133.37	0	127.79	179.8	-0.12664
2	2	4	846.37	0	866.91	1084.8	-1.0583
2	2.5	2	13.1	0	15.327	14.118	-1.0891
2	2.5	3	35.8	0	38.741	39.952	-0.78591
2	3	2	9.98	0	10.172	8.5899	0.001486
2	3	3	44.6	0	44.272	42.63	0.081717
2	3.5	2	7.72	0	6.7502	5.2265	1.1734
2	3.5	3	41.4	0	46.324	42.354	-1.0325
2	4	2	4.2	0	4.4797	3.18	-0.12375
2	4	3	45.8	0	45.956	40.405	0.076455
2	4	5	785.03	0	759.17	867.44	-0.53219
2	4	4	1169.7	0	1172.7	1376	-0.47329
2	4.5	2	3.14	0	2.9729	1.9348	0.50166
2	4.5	3	47	0	44.083	37.627	0.83817
2	5	2	2	0	1.9729	1.1772	0.24913
2	5	3	42.4	0	41.37	34.529	0.45484
2	6	2	1.234	0	0.86891	0.43581	0.87981
2	6	3	38.2	0	35.049	28.408	1.1578

2	8	2	0.406	0	0.16854	0.059727	0.54318
2	8	3	26	0	23.613	18.721	1.2278
2	8	4	1257.8	0	1243.5	1421.4	0.008037
2	8	5	1950.8	0	1814.3	1844.5	0.27071
2	10	3	16.8	0	15.766	12.519	0.7549
2	12	3	10.12	0	10.819	8.6856	-0.60114
2	12	4	1263.1	0	1246.2	1422.3	0.062589
2	12	5	2473.8	0	2303.2	2281.5	0.46663
2	24	3	2.5	0	2.804	2.4031	-0.66748
2	24	4	1263.1	0	1246.3	1422.3	0.062958
2	24	5	2835.5	0	2779.2	2724.9	0.18845
2	36	3	1.716	0	1.5894	1.3776	0.2267
2	36	5	2917	0	2968.5	2908.6	-0.06765
2	48	3	0.934	0	0.99159	0.86159	-0.16366
2	48	5	2944.8	0	3082.6	3020.1	-0.25902
3	0	1	0	7640	0	0	0
3	0.167	3	0.41	0	5.95E-05	2.39E-05	0.94621
3	0.167	2	0.914	0	0.64514	0.45353	0.61561
3	0.333	2	14.4	0	15.384	14.088	-0.54266
3	0.5	3	1.354	0	0.35708	0.20158	2.3331
3	0.5	2	40.6	0	39.524	42.996	-0.30213
3	0.75	3	3.2	0	2.9898	1.933	0.54164
3	0.75	2	52	0	51.832	62.559	-0.27016
3	1	3	9.2	0	9.1993	6.4154	-0.06021
3	1	2	46	0	47.104	57.26	-0.07279
3	1.25	3	12.9	0	17.906	13.034	-3.1448
3	1.25	2	37.4	0	39.263	46.624	0.068154
3	1.5	3	26.8	0	27.252	20.334	-0.6351
3	1.5	2	31.8	0	31.991	36.806	0.62135
3	2	2	19.8	0	20.936	22.492	0.58721
3	2	3	46	0	42.911	32.746	0.46426
3	2	5	229.91	0	167.53	179.8	2.7905
3	2	4	831.91	0	688.64	1084.8	1.3764
3	2.5	2	12.48	0	13.661	13.69	0.50078
3	2.5	3	51.4	0	52.02	39.952	-0.0662
3	3	2	10.76	0	8.9115	8.3296	2.5619
3	3	3	54.4	0	55.464	42.63	0.11439
3	3.5	2	6.4	0	5.8133	5.0681	1.6448
3	3.5	3	60	0	55.124	42.354	1.3692
3	4	2	4.12	0	3.7922	3.0836	1.3023
3	4	3	54.6	0	52.559	40.405	0.92261
3	4	5	456.47	0	787.03	867.44	-2.1146
3	4	4	853.57	0	908.11	1376	-1.2077

3	4.5	2	2.76	0	2.4738	1.8762	1.1493
3	4.5	3	56.2	0	48.832	37.627	2.0621
3	5	2	1.61	0	1.6137	1.1416	0.48834
3	5	3	47.6	0	44.617	34.529	1.1429
3	6	2	1.044	0	0.68671	0.4226	1.0131
3	6	3	37	0	36.178	28.408	0.48244
3	8	2	0.6	0	0.12435	0.057917	1.0778
3	8	3	21.2	0	22.779	18.721	-0.93986
3	8	4	889.09	0	955.06	1421.4	-0.82638
3	8	5	1472.9	0	1648.3	1844.5	-0.07752
3	10	3	14.26	0	14.428	12.519	-0.67798
3	12	3	8.74	0	9.5148	8.6856	-1.4358
3	12	4	889.09	0	956.6	1422.3	-0.81282
3	12	5	1913.7	0	1999.5	2281.5	0.11211
3	24	3	2.78	0	2.4132	2.4031	0.41047
3	24	4	889.09	0	956.65	1422.3	-0.81169
3	24	5	2224.7	0	2316.4	2724.9	-0.22239
3	36	3	1.542	0	1.3775	1.3776	0.16539
3	36	5	2287.5	0	2444.1	2908.6	-0.52942
3	48	3	1.284	0	0.84209	0.86159	0.87027
3	48	5	2321.1	0	2520.5	3020.1	-0.71381
4	0	1	0	7640	0	0	0
4	0.167	2	0.906	0	0.44033	0.34248	1.0761
4	0.333	2	11	0	11.858	10.638	-0.04527
4	0.5	3	0.834	0	0.57689	0.20158	0.84011
4	0.5	2	30	0	32.988	32.469	-0.80584
4	0.75	3	5.6	0	4.384	1.933	3.0514
4	0.75	2	51.6	0	45.346	47.242	0.61366
4	1	3	12.14	0	12.007	6.4154	1.2911
4	1	2	50.2	0	41.149	43.24	1.3498
4	1.25	3	16.58	0	20.889	13.034	-1.258
4	1.25	2	34.6	0	33.601	35.208	0.096966
4	1.5	3	23.4	0	28.828	20.334	-1.4853
4	1.5	2	26.6	0	26.628	27.794	0.008366
4	2	2	12.12	0	16.376	16.985	-1.6898
4	2	3	38.6	0	39.215	32.746	-0.20115
4	2	5	302.77	0	289.28	179.8	0.48201
4	2	4	855.64	0	839.05	1084.8	-0.54661
4	2.5	2	8.92	0	10.022	10.338	-0.45646
4	2.5	3	43	0	43.302	39.952	-0.27558
4	3	2	6.1	0	6.1311	6.2901	0.31112
4	3	3	39.4	0	43.5	42.63	-1.1898
4	3.5	2	4.26	0	3.7505	3.8272	1.0472

4	3.5	3	44.6	0	41.581	42.354	0.55329
4	4	2	2.64	0	2.2942	2.3286	0.85722
4	4	3	44.2	0	38.626	40.405	1.3433
4	4	4	1060.6	0	1064.8	1376	-0.44938
4	4	5	1250.9	0	1093.5	867.44	1.0227
4	4.5	2	1.37	0	1.4034	1.4168	0.11314
4	4.5	3	38.8	0	35.266	37.627	0.95496
4	5	2	0.794	0	0.85844	0.86205	-0.00538
4	5	3	33.4	0	31.858	34.529	0.48642
4	6	2	0.566	0	0.32121	0.31913	0.57791
4	6	3	24.4	0	25.567	28.408	-0.36754
4	8	3	16.66	0	16.218	18.721	0.47766
4	8	4	1092.7	0	1100.8	1421.4	-0.35012
4	8	5	2170.9	0	2097.5	1844.5	0.33683
4	10	3	10.62	0	10.523	12.519	0.32235
4	12	3	6.66	0	7.1385	8.6856	-0.36412
4	12	4	1100.9	0	1101.5	1422.3	-0.2471
4	12	5	2636.2	0	2514.8	2281.5	0.46632
4	24	3	2.28	0	1.9616	2.4031	0.75756
4	24	4	1100.9	0	1101.5	1422.3	-0.24708
4	24	5	2884.3	0	2921.1	2724.9	0.036855
4	36	3	1.036	0	1.1288	1.3776	-0.15795
4	36	5	2959.1	0	3091.4	2908.6	-0.18181
4	48	3	0.906	0	0.69611	0.86159	0.51229
4	48	5	2975.9	0	3194.1	3020.1	-0.36817
5	0	1	0	7640	0	0	0
5	0.5	2	2.32	0	4.11	33.783	-3.0679
5	0.75	2	21.8	0	18.668	49.154	0.21602
5	1	3	1.106	0	1.0939	6.4154	-0.00094
5	1	2	37	0	32.752	44.99	0.51873
5	1.25	3	4.24	0	3.4775	13.034	1.3411
5	1.25	2	40	0	36.734	36.633	0.7573
5	1.5	3	6.6	0	7.4202	20.334	-1.0069
5	1.5	2	33.8	0	33.195	28.919	0.45582
5	2	3	17.1	0	17.433	32.746	-0.13692
5	2	2	20.6	0	21.428	17.672	-0.08331
5	2	5	65.938	0	66.145	179.8	-0.96634
5	2	4	514.27	0	528.43	1084.8	-1.7403
5	2.5	2	12.72	0	12.866	10.756	-0.08467
5	2.5	3	27.8	0	25.884	39.952	0.81896
5	3	2	7.24	0	7.6676	6.5447	-0.47894
5	3	3	28.4	0	30.792	42.63	-0.75056
5	3.5	2	4.28	0	4.5671	3.9821	-0.48796

5	3.5	3	32.2	0	32.64	42.354	-0.12361
5	4	2	3.02	0	2.7202	2.4228	0.40971
5	4	3	31.8	0	32.474	40.405	-0.20284
5	4	5	578.86	0	530.45	867.44	-0.68548
5	4	4	751.19	0	763.19	1376	-0.92797
5	4.5	2	1.814	0	1.6202	1.4742	0.30759
5	4.5	3	29.4	0	31.157	37.627	-0.54874
5	5	2	0.808	0	0.96503	0.89694	-0.36485
5	5	3	27.8	0	29.26	34.529	-0.44916
5	6	2	0.54	0	0.34235	0.33205	0.39934
5	6	3	23.2	0	24.967	28.408	-0.56669
5	8	4	802.2	0	796.51	1421.4	-0.59116
5	8	5	1505.9	0	1338.5	1844.5	0.11274
5	8.033	3	19.22	0	17.346	18.593	1.4038
5	10	3	13.86	0	12.275	12.519	1.6655
5	12	4	808.68	0	797.03	1422.3	-0.48708
5	12	5	1977.5	0	1743.9	2281.5	0.4748
5	12.083	3	10.04	0	8.7698	8.563	1.7598
5	24	3	2.22	0	2.6183	2.4031	-0.56961
5	24	4	808.68	0	797.04	1422.3	-0.4873
5	24	5	2059.5	0	2195.9	2724.9	-0.61762
5	36	3	0.784	0	1.5036	1.3776	-1.4381
5	36	5	2132.9	0	2386.3	2908.6	-0.82265
5	48	5	2160.2	0	2503.5	3020.1	-0.98214
6	0	1	0	7640	0	0	0
6	0.333	3	0.35	0	0.01837	0.010988	0.76125
6	0.333	2	8.42	0	8.2754	13.754	-0.44688
6	0.5	3	0.764	0	0.35146	0.20158	0.89739
6	0.5	2	31	0	27.971	41.979	0.3478
6	0.75	3	2.8	0	3.411	1.933	-1.3668
6	0.75	2	37.4	0	43.307	61.079	-1.3091
6	1	3	10.5	0	11.024	6.4154	-0.8101
6	1	2	36.6	0	39.266	55.905	-0.82869
6	1.25	3	20	0	21.411	13.034	-0.96471
6	1.25	2	31.6	0	30.756	45.521	-0.17954
6	1.5	2	25.8	0	23.131	35.935	0.45995
6	1.5	3	38.6	0	31.735	20.334	2.0107
6	2	2	13.06	0	12.741	21.959	-0.11565
6	2	3	48.6	0	46.293	32.746	0.49205
6	2	5	322.24	0	304.82	179.8	0.39954
6	2	4	742.52	0	770.2	1084.8	-0.94016
6	2.5	2	5.86	0	6.9781	13.366	-1.2244
6	2.5	3	53.8	0	51.984	39.952	0.42489

6	3.017	2	3.44	0	3.7425	7.9962	-0.48114
6	3.017	3	47.2	0	51.812	42.661	-0.80909
6	3.5	2	2.2	0	2.091	4.9481	0.20947
6	3.5	3	47.8	0	48.813	42.354	-0.09729
6	4	2	1.574	0	1.1446	3.0106	0.89265
6	4	3	48.4	0	44.501	40.405	1.0166
6	4	4	903.38	0	925.71	1376	-0.95728
6	4	5	1279.5	0	1232.9	867.44	0.61871
6	4.5	2	1.37	0	0.62656	1.8318	1.578
6	4.5	3	39.6	0	39.865	37.627	0.055306
6	5	2	0.752	0	0.34298	1.1145	0.88326
6	5	3	34.8	0	35.364	34.529	-0.03664
6	6	2	0.422	0	0.10277	0.4126	0.68621
6	6	3	26	0	27.474	28.408	-0.41033
6	8	3	15.54	0	16.554	18.721	-0.46052
6	8	4	958.35	0	940.93	1421.4	-0.39681
6	8	5	2522.2	0	2296.7	1844.5	0.99553
6	10	3	9.92	0	10.335	12.519	-0.23491
6	12	3	7.7	0	6.8188	8.6856	1.2374
6	12	4	964.56	0	941.05	1422.3	-0.30592
6	12	5	2834	0	2698.4	2281.5	0.55523
6	24	3	2.18	0	1.8502	2.4031	0.73837
6	24	4	964.56	0	941.06	1422.3	-0.30594
6	24	5	3077.7	0	3069.7	2724.9	0.10584
6	36	3	0.992	0	1.0661	1.3776	-0.14636
6	36	5	3149	0	3226.7	2908.6	-0.12278
6	48	5	3179.4	0	3320.5	3020.1	-0.27844
6	48.15	3	0.552	0	0.64446	0.85661	-0.19793
7	0	1	0	7640	0	0	0
7	0.167	2	1.206	0	0.31159	0.52148	1.9885
7	0.333	3	0.36	0	0.003087	0.010988	0.82508
7	0.333	2	10.16	0	9.4361	16.199	1.6439
7	0.5	3	0.354	0	0.055325	0.20158	0.7067
7	0.5	2	24.2	0	30.319	49.438	-0.84628
7	0.75	3	0.956	0	0.53442	1.933	1.0786
7	0.75	2	47.6	0	52.377	71.932	-0.76275
7	1	3	1.724	0	1.8363	6.4154	0.017298
7	1	2	59	0	57.79	65.839	0.006158
7	1.25	3	4.9	0	3.9023	13.034	2.0694
7	1.25	2	67.4	0	54.718	53.61	1.6893
7	1.5	3	4.52	0	6.3794	20.334	-2.1507
7	1.5	2	56	0	48.374	42.32	1.237
7	2	3	10.9	0	11.207	32.746	-0.16495

7	2	2	31	0	34.483	25.862	-0.6149
7	2	5	50.017	0	51.304	179.8	-0.54291
7	2	4	1190.7	0	1183.9	1084.8	-0.44508
7	2.5	3	16.14	0	14.726	39.952	0.86801
7	2.5	2	25	0	23.343	15.741	0.62731
7	3	3	15.16	0	16.736	42.63	-1.0931
7	3	2	15.22	0	15.502	9.5776	-0.09543
7	3.5	2	10.28	0	10.219	5.8274	0.039454
7	3.5	3	18.56	0	17.566	42.354	0.39836
7	4	2	5.62	0	6.7167	3.5456	-1.0959
7	4	3	19.02	0	17.598	40.405	0.6778
7	4	5	332.23	0	293.51	867.44	-0.26862
7	4	4	1688.5	0	1717.2	1376	-0.01296
7	4.5	2	4.42	0	4.4094	2.1573	0.008852
7	4.5	3	17.2	0	17.134	37.627	-0.02316
7	5	2	2.94	0	2.8934	1.3126	0.081819
7	5	3	15.78	0	16.385	34.529	-0.3447
7	6.117	2	1.434	0	1.1283	0.43259	0.63113
7	6.117	3	8.02	0	14.306	27.735	-4.0816
7	8	2	1.406	0	0.23058	0.066594	2.4943
7	8	3	10.9	0	10.913	18.721	0.55296
7	8	5	819.39	0	733.03	1844.5	-0.47629
7	8	4	1825.3	0	1836.5	1421.4	0.27331
7	10.033	2	0.756	0	0.041522	0.008832	1.5172
7	10.033	3	7.38	0	8.1233	12.439	-0.01103
7	12	5	1115.9	0	984.98	2281.5	-0.25533
7	12	4	1884.9	0	1840.6	1422.3	0.70268
7	12.033	2	0.426	0	0.007688	0.00121	0.88774
7	12.033	3	8.48	0	6.1951	8.6366	4.0183
7	24	5	1126	0	1307.3	2724.9	-1.9492
7	24	4	1886	0	1840.8	1422.3	0.70962
7	24.05	3	2.06	0	2.1062	2.3959	0.61873
7	36	3	1.236	0	1.247	1.3776	0.45973
7	36	5	1234.6	0	1453.8	2908.6	-1.8941
7	48	3	0.854	0	0.83012	0.86159	0.41246
7	48	5	1277.1	0	1546.8	3020.1	-1.9771
8	0	1	0	7640	0	0	0
8	0.333	2	5.38	0	6.35	17.543	-2.151
8	0.5	2	36	0	31.744	53.543	-0.99907
8	0.75	3	0.806	0	1.186	1.933	-1.1533
8	0.75	2	80.4	0	68.928	77.904	0.46323
8	1	3	3.6	0	4.9241	6.4154	-2.9394
8	1	2	76.4	0	69.749	71.305	0.96088

8	1.25	3	11.24	0	11.326	13.034	-1.3398
8	1.25	2	56.8	0	54.844	58.06	0.62992
8	1.5	3	19.24	0	18.859	20.334	-1.0272
8	1.5	2	38.6	0	40.291	45.834	-0.17201
8	2	2	17.44	0	21.091	28.009	-1.4674
8	2	3	35.6	0	31.676	32.746	0.64584
8	2	5	222.06	0	168.97	179.8	0.98193
8	2	4	1240.8	0	1222.5	1084.8	0.69078
8	2.5	2	9.46	0	11.008	17.048	-1.2255
8	2.5	3	40.4	0	38.317	39.952	0.50529
8	3	2	5.74	0	5.7446	10.373	-0.1518
8	3	3	39	0	39.833	42.63	0.054019
8	3.5	2	3.26	0	2.998	6.3112	0.34283
8	3.5	3	37	0	38.371	42.354	0.032496
8	4	2	1.796	0	1.5646	3.84	0.40342
8	4	3	31.4	0	35.507	40.405	-0.76026
8	4	5	805.72	0	826.12	867.44	0.34391
8	4	4	1457.7	0	1461.4	1376	0.020976
8	4.5	2	1.414	0	0.8165	2.3364	1.2081
8	4.5	3	38.6	0	32.151	37.627	2.4316
8	5	2	0.758	0	0.42611	1.4216	0.68299
8	5	3	27	0	28.772	34.529	-0.29053
8	6	2	0.488	0	0.11605	0.52626	0.783
8	6	3	23	0	22.701	28.408	0.34881
8	8	3	13.3	0	14.08	18.721	-0.51553
8	8	4	1485.4	0	1480.5	1421.4	-0.05926
8	8	5	1516.4	0	1641.8	1844.5	-0.08541
8	10.017	3	9.32	0	8.9833	12.478	0.26382
8	12	4	1494.1	0	1480.6	1422.3	0.020872
8	12	5	1795.5	0	1967.4	2281.5	-0.34244
8	12.017	3	6.58	0	6.0416	8.6603	0.60783
8	24	3	1.706	0	1.6428	2.4031	0.056054
8	24	4	1494.1	0	1480.6	1422.3	0.020846
8	24	5	2088.6	0	2277.9	2724.9	-0.51712
8	36	5	2155.9	0	2407.5	2908.6	-0.74744
8	36.017	3	0.75	0	0.9438	1.3767	-0.48648
8	48	5	2183.3	0	2485.4	3020.1	-0.91622
9	0	1	0	7640	0	0	0
9	0.167	2	2.24	0	1.6458	0.52885	1.7568
9	0.333	2	31.2	0	34.229	16.428	0.66779
9	0.5	3	0.362	0	0.074036	0.20158	0.67131
9	0.5	2	76.6	0	82.766	50.137	-0.14256
9	0.75	3	0.882	0	0.66873	1.933	0.48184

9	0.75	2	118.2	0	108.28	72.949	0.83853
9	1	3	2.34	0	2.2989	6.4154	-0.0251
9	1	2	118.6	0	100.22	66.77	1.6713
9	1.25	3	5.2	0	5.0402	13.034	-0.06151
9	1.25	2	94.8	0	84.082	54.368	1.323
9	1.5	3	6.84	0	8.6057	20.334	-2.3748
9	1.5	2	70.4	0	68.168	42.918	0.57925
9	2	3	17.26	0	16.573	32.746	-0.25286
9	2	2	42	0	43.433	26.227	-0.11178
9	2	5	83.624	0	66.171	179.8	0.46774
9	2	4	1575.6	0	1584.9	1084.8	0.53063
9	2.5	3	21.2	0	23.551	39.952	-1.5803
9	2.5	2	26.2	0	27.4	15.963	-0.37431
9	3	2	15.5	0	17.258	9.713	-0.90383
9	3	3	26.6	0	28.378	42.63	-1.0125
9	3.5	2	9.96	0	10.867	5.9098	-0.79571
9	3.5	3	31.4	0	30.995	42.354	-0.03764
9	4	2	7.78	0	6.8424	3.5957	0.70543
9	4	3	33.4	0	31.827	40.405	0.50948
9	4	5	467.43	0	449.27	867.44	-0.86006
9	4	4	2067	0	2056	1376	0.61652
9	4.5	2	4.68	0	4.3083	2.1878	0.30941
9	4.5	3	34.8	0	31.399	37.627	1.2468
9	5	2	2.56	0	2.7128	1.3311	-0.41704
9	5	3	31	0	30.171	34.529	0.52562
9	6	2	1.032	0	1.0755	0.49279	-0.18052
9	6	3	25.2	0	26.59	28.408	-0.16194
9	8	5	1321.4	0	1197.7	1844.5	0.35955
9	8	4	2161.3	0	2141.8	1421.4	0.58406
9	8.1	3	19.16	0	18.851	18.337	0.61286
9	10	3	14.32	0	13.657	12.519	0.92578
9	12	5	1370.7	0	1594.6	2281.5	-1.1635
9	12	4	2171.2	0	2143.9	1422.3	0.63019
9	12.5	3	10.18	0	9.2216	7.9823	1.381
9	24	3	3	0	2.9196	2.4031	0.3713
9	24	5	1781	0	2041.1	2724.9	-0.83231
9	24	4	2171.2	0	2143.9	1422.3	0.62959
9	36	3	1.586	0	1.6709	1.3776	-0.05115
9	36	5	1898	0	2227.8	2908.6	-0.91294
9	48	3	1.166	0	1.078	0.86159	0.29166
9	48	5	1940.6	0	2342.9	3020.1	-1.0469
10	0	1	0	7640	0	0	0
10	0.167	2	6.16	0	5.3796	0.52699	3.3202

10	0.333	3	0.482	0	0.075795	0.010988	1.0052
10	0.333	2	32.4	0	45.412	16.37	0.8568
10	0.5	3	0.996	0	0.70539	0.20158	1.1549
10	0.5	2	68	0	73.378	49.961	0.71391
10	0.75	3	3.86	0	3.7735	1.933	1.8861
10	0.75	2	93.8	0	80.274	72.692	1.2894
10	1	3	9.44	0	9.1344	6.4154	2.7936
10	1	2	89.6	0	70.64	66.535	1.3449
10	1.25	3	15.52	0	15.387	13.034	2.6593
10	1.25	2	69	0	57.409	54.176	0.37831
10	1.5	3	22.8	0	21.278	20.334	3.0142
10	1.5	2	47	0	45.024	42.767	-1.1401
10	2	5	8.1559	0	161.69	179.8	-1.9374
10	2	2	23.4	0	26.515	26.135	-2.7364
10	2	3	28.4	0	29.791	32.746	0.90067
10	2	4	783.61	0	1312.3	1084.8	-3.105
10	2.5	2	12.36	0	15.302	15.907	-3.3451
10	2.5	3	31.6	0	33.817	39.952	-0.16311
10	3	2	7.26	0	8.7824	9.6788	-2.9744
10	3	3	34.4	0	34.745	42.63	-0.25931
10	3.5	2	4.76	0	5.0329	5.889	-1.7953
10	3.5	3	35.6	0	33.901	42.354	-0.12006
10	4	2	2.98	0	2.8829	3.5831	-0.95879
10	4	3	31.2	0	32.155	40.405	-1.2606
10	4	5	416.19	0	637.89	867.44	-1.2097
10	4	4	1599.7	0	1594	1376	0.37858
10	5	2	1.12	0	0.9457	1.3265	-0.18501
10	5	3	29.4	0	27.767	34.529	-0.72899
10	6	2	0.628	0	0.31021	0.49105	0.44151
10	6	3	24.2	0	23.463	28.408	-1.1625
10	8	3	18.06	0	16.634	18.721	-0.689
10	8	5	975.75	0	1314.3	1844.5	-2.2524
10	8	4	1712	0	1627.8	1421.4	0.57992
10	10	3	12.2	0	12.021	12.519	-1.3544
10	12	4	1779.8	0	1628.1	1422.3	1.1552
10	12	5	2031.1	0	1663.1	2281.5	0.96978
10	12.033	3	7.18	0	8.9087	8.6366	-3.2016
10	24	3	3.2	0	2.9297	2.4031	-0.28496
10	24	4	1790.1	0	1628.1	1422.3	1.2453
10	24	5	2271.8	0	2086.1	2724.9	-0.04231
10	36	3	1.494	0	1.7201	1.3776	-1.0085
10	36	5	2425.4	0	2276	2908.6	-0.17675
10	48	3	1.078	0	1.1194	0.86159	-0.46492

10	48	5	2472.4	0	2394.9	3020.1	-0.39001
11	0	1	0	7640	0	0	0
11	0.333	2	3.74	0	3.9283	14.759	-0.86552
11	0.517	2	26.2	0	25.653	47.723	-0.90174
11	0.75	3	1.016	0	1.2642	1.933	-0.66925
11	0.75	2	67.4	0	61.794	65.538	0.43364
11	1	3	4.02	0	4.7655	6.4154	-1.4321
11	1	2	73	0	75.525	59.987	0.40437
11	1.25	3	9.26	0	9.9676	13.034	-0.94257
11	1.25	2	71.4	0	69.635	48.845	1.1423
11	1.5	3	18.14	0	15.341	20.334	1.5774
11	1.5	2	61.8	0	58.861	38.558	1.3082
11	2	3	25	0	23.592	32.746	0.48731
11	2	2	39.4	0	40.074	23.563	0.62534
11	2	5	111.56	0	92.169	179.8	0.96159
11	2	4	947.23	0	939.27	1084.8	-0.94128
11	2.5	2	29.4	0	27.109	14.342	1.2244
11	2.5	3	29.6	0	28.209	39.952	0.4819
11	3	2	18.02	0	18.335	8.7263	0.34807
11	3	3	29.8	0	30.265	42.63	-0.07878
11	3.5	2	13.04	0	12.4	5.3094	0.75075
11	3.5	3	30.6	0	30.681	42.354	0.14424
11	4	2	7.8	0	8.3867	3.2305	-0.18035
11	4	3	28.2	0	30.083	40.405	-0.3763
11	4	5	538.1	0	433.68	867.44	1.2825
11	4	4	1389.6	0	1363.5	1376	0.25104
11	4.5	2	5.92	0	5.6722	1.9655	0.51929
11	4.5	3	27.6	0	28.885	37.627	-0.10786
11	5	2	3.7	0	3.8363	1.1959	-0.00555
11	5	3	26	0	27.357	34.529	-0.08162
11	6	2	2.22	0	1.7548	0.44273	0.99806
11	6	3	23.2	0	23.957	28.408	0.23977
11	8	2	1.972	0	0.36718	0.060675	3.4219
11	8	3	17.3	0	17.689	18.721	0.53734
11	10	2	0.684	0	0.07683	0.008315	1.2977
11	10	3	13.02	0	13.037	12.519	0.8446
11	12	3	10.48	0	9.8073	8.6856	1.5228
11	12	5	955.23	0	1306.6	2281.5	-2.2282
11	12	4	1451	0	1475.6	1422.3	0.10886
11	24	3	4.02	0	3.2137	2.4031	2.0555
11	24	5	1410.5	0	1690.9	2724.9	-1.2605
11	24	4	1470.8	0	1475.8	1422.3	0.29902
11	36	3	2.1	0	1.8825	1.3776	0.81656

11	36	5	1562	0	1862.2	2908.6	-1.1333
11	48	3	1.418	0	1.2375	0.86159	0.65827
11	48	5	1608.4	0	1970	3020.1	-1.2387
12	0	1	0	7640	0	0	0
12	0.167	2	0.654	0	0.87747	0.39804	-0.2419
12	0.333	2	15.94	0	17.2	12.364	-0.00807
12	0.5	2	40.4	0	39.015	37.736	0.11457
12	0.75	3	4.64	0	2.695	1.933	4.6873
12	0.75	2	50	0	47.188	54.906	-0.1282
12	1	3	6.6	0	7.3964	6.4154	0.16447
12	1	2	46.8	0	41.855	50.255	0.36042
12	1.25	3	11.52	0	13.227	13.034	-0.40426
12	1.25	2	34.2	0	34.623	40.92	-0.46711
12	1.5	3	15.64	0	18.896	20.334	-1.2567
12	1.5	2	28.8	0	28.135	32.303	-0.0572
12	2	2	17.96	0	18.38	19.74	-0.17927
12	2	3	23.8	0	27.431	32.746	-1.4731
12	2	5	206.55	0	195.56	179.8	0.30793
12	2	4	927.12	0	895.92	1084.8	-0.2773
12	2.5	2	11.36	0	11.982	12.015	-0.24762
12	2.5	3	30.8	0	31.913	39.952	-0.76952
12	3	2	7.54	0	7.8096	7.3106	-0.04334
12	3	3	31.8	0	33.443	42.63	-0.99982
12	3.5	2	5.44	0	5.0902	4.448	0.63244
12	3.5	3	35.2	0	33.132	42.354	0.15626
12	4	2	3.1	0	3.3177	2.7064	-0.1407
12	4	3	33.2	0	31.757	40.405	0.052041
12	4	5	894.34	0	827.07	867.44	-0.05806
12	4	4	1159.1	0	1170.5	1376	-0.47462
12	4.5	2	2.56	0	2.1624	1.6467	0.88826
12	4.5	3	31.6	0	29.822	37.627	0.28689
12	5	2	1.25	0	1.4095	1.0019	-0.17622
12	5	3	28.6	0	27.638	34.529	0.13155
12	6	2	0.794	0	0.59877	0.3709	0.49105
12	6	3	25.8	0	23.211	28.408	1.0918
12	8	3	16.6	0	15.865	18.721	0.70386
12	8	4	1218.4	0	1229	1421.4	-0.18862
12	8	5	1947.1	0	1747.6	1844.5	0.38852
12	10	3	10.88	0	10.921	12.519	0.35893
12	12	3	7.52	0	7.7511	8.6856	0.18334
12	12	4	1228.4	0	1230.9	1422.3	-0.07581
12	12	5	2358.8	0	2187.7	2281.5	0.30689
12	24	3	2.42	0	2.2292	2.4031	0.65463

12	24	4	1228.4	0	1230.9	1422.3	-0.07548
12	24	5	2677.6	0	2658.2	2724.9	0.005124
12	36	5	2742.9	0	2855.8	2908.6	-0.26147
12	36.017	3	1.09	0	1.2804	1.3767	-0.26286
12	48	3	1.178	0	0.81059	0.86159	0.94677
12	48	5	2781.9	0	2976.6	3020.1	-0.40707
13	0	1	0	7640	0	0	0
13	0.167	2	0.496	0	0.39782	0.41117	0.26664
13	0.333	2	8.56	0	8.2675	12.772	0.3357
13	0.5	3	0.412	0	0.048865	0.20158	0.83897
13	0.5	2	18.82	0	20.935	38.98	-1.4756
13	0.75	3	0.864	0	0.4504	1.933	0.93225
13	0.75	2	30.2	0	30.39	56.716	-1.2502
13	1	3	1.62	0	1.5914	6.4154	-0.04237
13	1	2	31.4	0	30.714	51.912	-0.81842
13	1.25	3	2.92	0	3.5821	13.034	-1.4753
13	1.25	2	27.6	0	27.23	42.269	-0.53579
13	1.5	3	6.36	0	6.2543	20.334	-0.37688
13	1.5	2	21.8	0	22.654	33.368	-0.61838
13	2	3	10.54	0	12.425	32.746	-2.3573
13	2	2	14.52	0	14.283	20.391	0.098828
13	2	5	109.28	0	82.184	179.8	0.39269
13	2	4	1244.3	0	1142.5	1084.8	0.56988
13	2.5	2	9.42	0	8.4943	12.411	0.77785
13	2.5	3	17.14	0	17.935	39.952	-1.4509
13	3	2	4.7	0	4.9255	7.5516	-0.30613
13	3	3	21.2	0	21.715	42.63	-1.1882
13	3.5	2	3.02	0	2.8231	4.5947	0.25922
13	3.5	3	22.8	0	23.668	42.354	-1.1759
13	4	2	1.504	0	1.6093	2.7956	-0.27693
13	4	3	21.8	0	24.161	40.405	-1.6216
13	4	5	648.82	0	578.68	867.44	-0.70921
13	4	4	1472.7	0	1479.3	1376	0.13974
13	4.5	2	0.712	0	0.91495	1.701	-0.47925
13	4.5	3	25.2	0	23.658	37.627	0.19659
13	5	2	0.646	0	0.51954	1.0349	0.21816
13	5	3	23.8	0	22.558	34.529	0.25403
13	6	2	0.5	0	0.16726	0.38313	0.6821
13	6	3	19.82	0	19.625	28.408	0.07856
13	8	3	13.72	0	13.989	18.721	0.20664
13	8	4	1494.6	0	1519.3	1421.4	-0.01495
13	8	5	1538.3	0	1522.6	1844.5	-0.44494
13	10	3	10.26	0	9.9707	12.519	0.91934

13	12	3	9	0	7.2939	8.6856	2.816
13	12	4	1494.6	0	1519.8	1422.3	-0.02131
13	12	5	2013.9	0	2015.6	2281.5	-0.12912
13	24	3	2.64	0	2.1987	2.4031	1.4307
13	24	4	1494.6	0	1519.8	1422.3	-0.02141
13	24	5	2455.6	0	2580	2724.9	-0.06363
13	36	3	1.024	0	1.2654	1.3776	-0.20796
13	36	5	2580.2	0	2819.8	2908.6	-0.19
13	48	3	0.852	0	0.8191	0.86159	0.3112
13	48	5	2637	0	2968.3	3020.1	-0.30143
14	0	1	0	7640	0	0	0
14	0.167	2	0.554	0	0.36406	0.37416	0.44053
14	0.333	2	9.5	0	9.7442	11.623	0.65672
14	0.5	3	0.472	0	0.25636	0.20158	0.57788
14	0.5	2	28	0	29.021	35.472	1.0152
14	0.75	3	2.94	0	2.277	1.933	1.9547
14	0.75	2	56.8	0	47.809	51.612	2.3666
14	1	3	8.32	0	7.3966	6.4154	2.4151
14	1	2	61.4	0	51.909	47.24	1.7217
14	1.25	3	13.7	0	15.092	13.034	0.81422
14	1.25	2	46.8	0	48.633	38.465	-0.49163
14	1.5	3	23	0	23.9	20.334	1.4557
14	1.5	2	38.8	0	42.477	30.365	-1.3099
14	2	2	32	0	29.26	18.556	-0.54014
14	2	3	44.4	0	39.95	32.746	2.6792
14	2	5	89.869	0	176.06	179.8	-0.90732
14	2	4	574.94	0	920.27	1084.8	-3.2373
14	2.5	2	17.62	0	18.902	11.294	-1.988
14	2.5	3	48.2	0	50.409	39.952	0.54928
14	3	2	12.42	0	11.871	6.8719	-1.2184
14	3	3	52.6	0	55.248	42.63	-0.012
14	3.5	2	7.52	0	7.3571	4.1812	-1.3344
14	3.5	3	50.8	0	56.049	42.354	-0.89458
14	4	2	4.26	0	4.5306	2.544	-1.6621
14	4	3	56.8	0	54.366	40.405	0.22056
14	4	5	757.11	0	910.35	867.44	-1.0938
14	4	4	1204.8	0	1284.5	1376	-1.0157
14	4.5	2	2.26	0	2.7812	1.5479	-1.9298
14	4.5	3	50.4	0	51.325	37.627	-0.63257
14	5	2	1.308	0	1.7046	0.94178	-1.5576
14	5	3	53.2	0	47.655	34.529	0.60726
14	6	2	0.62	0	0.63914	0.34865	-0.43973
14	6	3	41.4	0	39.997	28.408	-0.34335

14	8	3	27.4	0	27.246	18.721	-0.57456
14	8	4	1472	0	1345.5	1421.4	0.76838
14	8	5	2318.3	0	2038.8	1844.5	0.51439
14	10	3	18.06	0	18.738	12.519	-0.81632
14	12	3	13.16	0	13.302	8.6856	-0.40497
14	12	4	1472	0	1346.7	1422.3	0.74067
14	12	5	2984.8	0	2576.7	2281.5	0.7901
14	24	3	3.96	0	3.808	2.4031	0.23076
14	24	4	1472	0	1346.7	1422.3	0.73999
14	24	5	3504.6	0	3151.2	2724.9	0.7061
14	36	3	1.912	0	2.1852	1.3776	-0.5839
14	36	5	3579.9	0	3391.3	2908.6	0.39868
14	48	3	1.282	0	1.3849	0.86159	-0.23554
14	48	5	3614.3	0	3538.2	3020.1	0.21228
15	0	1	0	7640	0	0	0
15	0.333	2	0.774	0	0.32117	11.83	1.1043
15	0.5	2	3.92	0	2.8	36.104	2.7401
15	0.75	3	0.522	0	0.053816	1.933	1.0926
15	0.75	2	12.7	0	13.366	52.531	0.84867
15	1	3	0.73	0	0.35551	6.4154	0.91591
15	1	2	18.04	0	26.86	48.081	-1.6571
15	1.25	3	1.81	0	1.22	13.034	1.4337
15	1.25	2	25.2	0	36.711	39.15	-1.8189
15	1.5	3	2.82	0	2.8613	20.334	0.08392
15	1.5	2	39.6	0	41.517	30.906	0.049919
15	2	3	7.12	0	8.2894	32.746	-1.2059
15	2	5	28.79	0	30.358	179.8	-0.56486
15	2	2	47.6	0	40.809	18.886	1.4915
15	2	4	648.94	0	673.9	1084.8	-1.9329
15	2.5	3	15.84	0	15.047	39.952	0.39843
15	2.5	2	42.2	0	34.026	11.495	1.9026
15	3	3	22.6	0	21.271	42.63	0.35726
15	3	2	30	0	26.15	6.9943	1.0695
15	3.5	2	21.2	0	19.148	4.2556	0.64856
15	3.5	3	25.6	0	25.943	42.354	-0.49252
15	4	2	14.36	0	13.581	2.5893	0.18852
15	4	3	31	0	28.832	40.405	0.37005
15	4	5	410.03	0	391.61	867.44	-1.1796
15	4	4	1458.9	0	1452.6	1376	-0.46113
15	4.5	2	9.82	0	9.4182	1.5754	0.022312
15	4.5	3	28.8	0	30.139	37.627	-0.84409
15	5	2	4.88	0	6.4239	0.95856	-1.8685
15	5	3	29.4	0	30.227	34.529	-0.64143

15	6	2	1.982	0	2.8848	0.35486	-1.7193
15	6	3	28.4	0	28.147	28.408	-0.1625
15	8	2	0.624	0	0.53366	0.048633	0.10857
15	8	3	19.5	0	21.196	18.721	-0.7564
15	8	5	1494.5	0	1359.5	1844.5	-0.49639
15	8	4	1717.6	0	1699.1	1421.4	0.42718
15	10	3	14.4	0	15.177	12.519	-0.17538
15	12	3	11.66	0	10.963	8.6856	1.1251
15	12	4	1739.3	0	1707.7	1422.3	0.57908
15	12	5	2066.3	0	1910.6	2281.5	-0.09956
15	24	3	3.22	0	3.021	2.4031	0.86172
15	24	4	1753.2	0	1708	1422.3	0.69384
15	24	5	2580.1	0	2510.4	2724.9	0.072882
15	36	3	2.16	0	1.6983	1.3776	1.3022
15	36	5	2688	0	2749.5	2908.6	-0.12311
15	48	3	1.188	0	1.0934	0.86159	0.43341
15	48	5	2727.6	0	2895.8	3020.1	-0.28953
16	0	1	0	7640	0	0	0
16	0.167	2	1.452	0	1.7394	0.43634	-0.78765
16	0.333	2	34	0	28.458	13.554	1.8267
16	0.5	2	54	0	55.837	41.367	0.20418
16	0.75	2	58.4	0	59.763	60.188	-0.21882
16	1	3	0.714	0	1.7735	6.4154	-2.447
16	1	2	55.6	0	51.106	55.09	0.48968
16	1.25	3	2.84	0	3.7829	13.034	-2.0053
16	1.25	2	45.6	0	42.363	44.857	0.44258
16	1.5	3	5.14	0	6.4001	20.334	-2.179
16	1.5	2	35.8	0	34.964	35.411	0.12635
16	2	3	14.9	0	12.469	32.746	1.186
16	2	2	23.4	0	23.786	21.639	-0.01297
16	2	5	53.881	0	60.088	179.8	-2.0772
16	2	4	1154.6	0	1135.4	1084.8	0.071786
16	2.5	2	13.42	0	16.18	13.171	-1.0017
16	2.5	3	20.6	0	18.243	39.952	0.59955
16	3	2	9.7	0	11.006	8.0139	-0.49187
16	3	3	23.4	0	22.719	42.63	-0.27008
16	3.5	2	6.3	0	7.4869	4.876	-0.65507
16	3.5	3	26.4	0	25.579	42.354	-0.08639
16	4	2	4.9	0	5.0928	2.9668	0.20349
16	4	3	27.6	0	26.924	40.405	0.006937
16	4	5	509.87	0	433.2	867.44	-0.30428
16	4	4	1460.3	0	1506.3	1376	-0.46282
16	4.5	2	3.96	0	3.4643	1.8051	1.163

16	4.5	3	28.6	0	27.04	37.627	0.48051
16	5	2	2.92	0	2.3565	1.0983	1.3546
16	5	3	27.2	0	26.261	34.529	0.37011
16	6	2	2.2	0	1.0904	0.40659	2.485
16	6	3	22.8	0	23.17	28.408	-0.02735
16	8	2	1.228	0	0.23346	0.055722	2.182
16	8	3	14.84	0	15.743	18.721	-0.45816
16	8	5	1192.8	0	1212.4	1844.5	-0.653
16	8	4	1591.9	0	1602.7	1421.4	0.080424
16	10	2	0.65	0	0.049986	0.007637	1.2946
16	10	3	8.32	0	10.103	12.519	-1.6895
16	12	3	6.92	0	6.5552	8.6856	0.34593
16	12	5	1552.9	0	1572.4	2281.5	-0.38785
16	12	4	1629.5	0	1607.2	1422.3	0.39626
16	24	3	1.936	0	1.421	2.4031	1.0254
16	24	4	1656.9	0	1607.4	1422.3	0.63807
16	24	5	1825.8	0	1872.1	2724.9	-0.63878
16	36	3	0.886	0	0.79262	1.3776	0.14963
16	36	5	1884.2	0	1981	2908.6	-0.93123
16	48	3	0.7	0	0.48398	0.86159	0.4542
16	48	5	1915.7	0	2045.5	3020.1	-1.108
17	0	1	0	7640	0	0	0
17	0.217	2	5.62	0	5.8503	1.4007	-0.18496
17	0.367	3	0.78	0	0.35974	0.023268	1.033
17	0.367	2	34	0	33.968	13.603	-0.11209
17	0.5	3	2.82	0	2.1934	0.20158	1.5962
17	0.5	2	56.4	0	53.161	29.684	0.11777
17	0.75	3	12.2	0	12.499	1.933	0.47544
17	0.75	2	55.4	0	54.469	43.19	-0.32025
17	1	3	28.6	0	28.321	6.4154	0.74937
17	1	2	46.2	0	42.92	39.531	0.19553
17	1.25	2	34.8	0	32.341	32.188	0.28609
17	1.25	3	42.6	0	43.332	13.034	0.26126
17	1.5	2	24.8	0	24.176	25.41	0.000415
17	1.5	3	45.6	0	54.626	20.334	-1.465
17	2	2	11.7	0	13.468	15.528	-0.99376
17	2	3	74.8	0	66.045	32.746	1.3365
17	2	5	681.76	0	663.72	179.8	1.0947
17	2	4	1284.3	0	1264.6	1084.8	0.1306
17	2.5	2	7.08	0	7.4995	9.451	-0.32613
17	2.5	3	65.2	0	67.583	39.952	-0.48003
17	3	2	4.1	0	4.1761	5.7506	-0.01329
17	3	3	61.8	0	64.151	42.63	-0.51617

17	3.5	2	2.32	0	2.3255	3.4989	0.080109
17	3.5	3	58.8	0	58.568	42.354	-0.09212
17	4	2	1.678	0	1.2949	2.1289	0.83583
17	4	3	54	0	52.325	40.405	0.21273
17	4	4	1477.2	0	1480.7	1376	-0.13129
17	4	5	2249.7	0	2074	867.44	1.4266
17	4.5	2	0.946	0	0.72108	1.2953	0.52099
17	4.5	3	47	0	46.173	37.627	0.086447
17	5	2	0.798	0	0.40153	0.7881	0.87261
17	5	3	42.8	0	40.464	34.529	0.50858
17	6	3	31.6	0	30.81	28.408	0.19608
17	8	4	1508.9	0	1503.5	1421.4	-0.03966
17	8	5	3845	0	3529.1	1844.5	1.4224
17	8.083	3	18.48	0	17.591	18.401	0.42797
17	10	3	11.16	0	10.955	12.519	0.08048
17	12	3	6.6	0	7.1253	8.6856	-0.74912
17	12	4	1508.9	0	1503.7	1422.3	-0.04141
17	12	5	4314	0	4046.2	2281.5	1.2059
17	24	3	1.902	0	1.9957	2.4031	-0.24938
17	24	4	1508.9	0	1503.7	1422.3	-0.04143
17	24	5	4606.3	0	4518.4	2724.9	0.82362
17	36	3	1.232	0	1.1538	1.3776	0.1428
17	36	5	4666.7	0	4724	2908.6	0.5857
17	48.383	3	0.868	0	0.68331	0.84893	0.40127
18	0	1	0	7640	0	0	0
18	0.333	2	3.92	0	3.927	14.393	-0.26921
18	0.5	2	18.84	0	18.299	43.928	-0.27193
18	0.75	3	0.972	0	0.47854	1.933	1.0922
18	0.75	2	41.4	0	41.295	63.915	-0.45986
18	1	3	2.04	0	2.1457	6.4154	-0.3718
18	1	2	46.2	0	48.464	58.501	-0.61977
18	1.25	3	5.38	0	5.4966	13.034	-0.4856
18	1.25	2	45	0	45.14	47.635	-0.11273
18	1.5	3	9.74	0	10.295	20.334	-0.97464
18	1.5	2	42	0	38.338	37.603	0.73539
18	2	3	21.6	0	21.615	32.746	-0.59521
18	2	2	24.6	0	24.948	22.979	0.005974
18	2	5	103.71	0	91.45	179.8	-0.60537
18	2	4	903.03	0	859	1084.8	-0.24041
18	2.5	2	15.84	0	15.508	13.986	0.27957
18	2.5	3	31	0	31.432	39.952	-0.64039
18	3	2	9	0	9.5216	8.5101	-0.27017
18	3	3	37.8	0	37.709	42.63	-0.30225

18	3.5	2	6.12	0	5.826	5.1779	0.42096
18	3.5	3	41.2	0	40.521	42.354	0.021724
18	4	2	4.02	0	3.5613	3.1505	0.7632
18	4	3	38.8	0	40.744	40.405	-0.48879
18	4	5	766.97	0	671.95	867.44	-0.03582
18	4	4	1163.7	0	1180.6	1376	-0.37272
18	4.5	2	1.948	0	2.1763	1.9169	-0.35156
18	4.5	3	41.6	0	39.31	37.627	0.70694
18	5	2	1.37	0	1.3299	1.1663	0.12681
18	5	3	37.8	0	36.949	34.529	0.42896
18	6	2	0.896	0	0.49654	0.43176	0.86526
18	6	3	33.6	0	31.247	28.408	1.0586
18	8	2	0.438	0	0.069222	0.059172	0.78825
18	8	3	22.2	0	20.985	18.721	0.94442
18	8	4	1211.1	0	1232	1421.4	-0.28942
18	8	5	1705.3	0	1695.1	1844.5	-0.01213
18	10	3	13.26	0	14.068	12.519	-0.18721
18	12	3	9.36	0	9.7265	8.6856	0.013866
18	12	4	1225.6	0	1233	1422.3	-0.13078
18	12	5	2140.9	0	2169.7	2281.5	0.0871
18	24	4	1235.1	0	1233.1	1422.3	-0.02144
18	24	5	2442.8	0	2641.1	2724.9	-0.23963
18	24.033	3	2.9	0	2.5634	2.3983	0.8473
18	36	3	1.628	0	1.4574	1.3776	0.4767
18	36	5	2507	0	2829.8	2908.6	-0.50542
18	48.033	3	1.482	0	0.91263	0.86049	1.3585
19	0	1	0	7640	0	0	0
19	0.167	2	1.488	0	0.7648	0.47064	1.7163
19	0.333	2	17.52	0	19.267	14.62	-0.17426
19	0.5	3	0.376	0	0.11711	0.20158	0.60428
19	0.5	2	52	0	51.084	44.619	0.04927
19	0.75	3	1.59	0	1.1237	1.933	1.0203
19	0.75	2	73.2	0	67.717	64.92	0.25549
19	1	3	3.64	0	3.9264	6.4154	-0.68131
19	1	2	64.4	0	60.951	59.421	0.14969
19	1.25	3	8.66	0	8.5879	13.034	-0.33075
19	1.25	2	53.8	0	50.037	48.384	0.41088
19	1.5	3	12.68	0	14.516	20.334	-1.8102
19	1.5	2	32.6	0	40.099	38.195	-1.4529
19	2	2	24.6	0	25.365	23.34	-0.17095
19	2	3	29	0	27.209	32.746	0.057403
19	2	5	156.6	0	127.75	179.8	0.24962
19	2	4	1258.3	0	1226.9	1084.8	0.32721

19	2.5	2	15.34	0	15.996	14.206	-0.20945
19	2.5	3	32.6	0	37.594	39.952	-1.7834
19	3	2	11.68	0	10.085	8.6439	1.2029
19	3	3	47.6	0	44.092	42.63	0.63648
19	3.5	2	6.94	0	6.3582	5.2593	0.65618
19	3.5	3	44.4	0	46.928	42.354	-0.49621
19	4	2	3.8	0	4.0086	3.2	-0.26361
19	4	3	43.2	0	46.994	40.405	-0.58823
19	4	5	840.1	0	811.63	867.44	-0.46331
19	4	4	1551.9	0	1580.2	1376	-0.15007
19	4.5	2	2.08	0	2.5272	1.947	-0.76015
19	4.5	3	56.6	0	45.232	37.627	2.9361
19	5	2	1.416	0	1.5933	1.1846	-0.33918
19	5	3	37	0	42.411	34.529	-0.8637
19	6	2	1.328	0	0.6333	0.43855	1.4506
19	6	3	37.6	0	35.587	28.408	1.0571
19	8	2	0.764	0	0.10005	0.060103	1.4077
19	8	3	24.4	0	23.253	18.721	0.84432
19	8	4	1642.8	0	1644.8	1421.4	0.15845
19	8	5	1981.8	0	1978.5	1844.5	0.22905
19	10	3	14.52	0	15.058	12.519	-0.17852
19	12	4	1659.6	0	1646.4	1422.3	0.29317
19	12	5	2512.7	0	2489.9	2281.5	0.46871
19	12.017	3	10.56	0	10.039	8.6603	0.53787
19	24	3	2.52	0	2.4979	2.4031	-0.01406
19	24	4	1672.4	0	1646.5	1422.3	0.40334
19	24	5	2845.9	0	2959.4	2724.9	0.13408
19	36	3	1.254	0	1.4141	1.3776	-0.3906
19	36	5	2926.9	0	3143.2	2908.6	-0.1107
19	48	3	1.138	0	0.87313	0.86159	0.57219
19	48	5	2957.2	0	3253.5	3020.1	-0.28789
20	0	1	0	7640	0	0	0
20	0.167	2	1.834	0	1.0148	0.41344	2.1789
20	0.333	2	17.66	0	21.035	12.843	-0.20785
20	0.5	2	52.2	0	49.918	39.196	0.36579
20	0.75	3	0.826	0	0.22334	1.933	1.4114
20	0.75	2	67.6	0	62.735	57.029	0.3453
20	1	3	1.184	0	0.80998	6.4154	0.87638
20	1	2	59	0	56.045	52.198	0.30134
20	1.25	3	2.24	0	1.8771	13.034	0.77235
20	1.25	2	49.2	0	45.798	42.503	0.55018
20	1.5	3	2.88	0	3.3901	20.334	-1.0001
20	1.5	2	37.2	0	36.404	33.552	0.16029

20	2	3	5.68	0	7.2914	32.746	-2.1916
20	2	2	22.6	0	22.51	20.504	-0.07608
20	2	5	37.738	0	34.162	179.8	-0.02218
20	2	4	1508.2	0	1466.8	1084.8	1.0429
20	2.5	3	13.2	0	11.494	39.952	0.99399
20	2.5	2	13.5	0	13.84	12.48	-0.3832
20	3	2	8.58	0	8.5031	7.5933	-0.19056
20	3	3	14.64	0	15.214	42.63	-0.92323
20	3.5	2	4.8	0	5.2239	4.6201	-0.75776
20	3.5	3	16.8	0	18.058	42.354	-1.3131
20	4	2	3.5	0	3.2093	2.811	0.2349
20	4	3	19.7	0	19.932	40.405	-0.75682
20	4	5	318.7	0	300.53	867.44	-1.3987
20	4	4	1840.8	0	1855.5	1376	0.2781
20	4.5	2	2	0	1.9716	1.7103	-0.12183
20	4.5	3	20.6	0	20.919	37.627	-0.78274
20	5	2	1.226	0	1.2113	1.0406	-0.09855
20	5	3	22.2	0	21.184	34.529	-0.11164
20	6	2	0.69	0	0.45717	0.38525	0.4274
20	6	3	20.4	0	20.251	28.408	-0.40332
20	8	2	0.42	0	0.065123	0.052797	0.73996
20	8	3	16.48	0	16.107	18.721	0.063328
20	8	5	1025.6	0	1011.2	1844.5	-1.4266
20	8	4	1907.8	0	1918.8	1421.4	0.204
20	10	3	12.48	0	12.102	12.519	0.44143
20	12	3	8.34	0	9.1184	8.6856	-0.41112
20	12	5	1476.2	0	1457.5	2281.5	-0.91084
20	12	4	1928.3	0	1920.1	1422.3	0.34088
20	24	3	3.58	0	2.8463	2.4031	1.9856
20	24	4	1958.8	0	1920.1	1422.3	0.5659
20	24	5	1977.8	0	2002.1	2724.9	-0.51314
20	36	3	1.758	0	1.6371	1.3776	0.65697
20	36	5	2127.5	0	2234.8	2908.6	-0.58594
20	48	3	1.388	0	1.0831	0.86159	0.98463
21	0	1	0	7640	0	0	0
21	0.167	2	6.92	0	6.4598	0.44411	1.2077
21	0.333	3	1.166	0	0.63574	0.010988	1.2511
21	0.333	2	44.8	0	48.027	13.795	-0.04005
21	0.5	3	4.1	0	4.8512	0.20158	-1.0795
21	0.5	2	63	0	62.528	42.103	-0.3263
21	0.75	3	20.2	0	19.086	1.933	0.76351
21	0.75	2	54.8	0	51.907	61.26	-0.04503
21	1	3	37.2	0	35.429	6.4154	0.72928

21	1	2	38.2	0	38.248	56.071	-0.34978
21	1.25	2	27.8	0	27.699	45.656	-0.21269
21	1.25	3	51	0	48.319	13.034	0.76289
21	1.5	2	20.6	0	20.005	36.041	0.058781
21	1.5	3	59.2	0	56.761	20.334	0.59547
21	2	2	9.62	0	10.425	22.025	-0.59893
21	2	3	63.6	0	63.523	32.746	0.11495
21	2	5	663.54	0	605.91	179.8	1.7821
21	2	4	907.34	0	913.96	1084.8	-0.36432
21	2.5	2	6.06	0	5.4324	13.405	0.73291
21	2.5	3	60.6	0	62.515	39.952	-0.22574
21	3	2	2.66	0	2.8308	8.1566	-0.25404
21	3	3	57.4	0	58.056	42.63	-0.02214
21	3.5	2	1.528	0	1.4751	4.9628	0.1351
21	3.5	3	49.2	0	52.355	42.354	-0.51126
21	4	2	1.056	0	0.76864	3.0196	0.62159
21	4	3	48.6	0	46.482	40.405	0.58474
21	4	4	1017.9	0	1023.9	1376	-0.60487
21	4	5	1791.5	0	1680.6	867.44	1.2042
21	4.5	2	0.6	0	0.40053	1.8372	0.43906
21	4.5	3	39.8	0	40.929	37.627	-0.15423
21	5	2	0.42	0	0.20871	1.1178	0.45978
21	5	3	36.4	0	35.894	34.529	0.27672
21	6	3	27.6	0	27.519	28.408	0.16016
21	8	3	17.14	0	16.437	18.721	0.51612
21	8	4	1036.8	0	1032.6	1421.4	-0.49264
21	8	5	2878.1	0	2766.1	1844.5	0.75696
21	10	3	10.24	0	10.279	12.519	0.007949
21	12	3	7.14	0	6.8385	8.6856	0.38943
21	12	4	1044.6	0	1032.6	1422.3	-0.3867
21	12	5	3271.8	0	3169.5	2281.5	0.60643
21	24	4	1044.6	0	1032.6	1422.3	-0.38671
21	24	5	3577.3	0	3557.2	2724.9	0.34691
21	24.267	3	2.04	0	1.9558	2.3653	0.16072
21	36	5	3655.9	0	3728	2908.6	0.14762
21	36.283	3	0.948	0	1.1372	1.3621	-0.43479
21	48	5	3690.6	0	3830.1	3020.1	0.012008
21	48.217	3	0.716	0	0.69116	0.8544	0.049231
22	0	1	0	7640	0	0	0
22	0.333	2	5.12	0	5.3494	13.17	-0.86062
22	0.5	3	0.76	0	0.28958	0.20158	1.1095
22	0.5	2	19.16	0	18.294	40.195	-0.44262
22	0.75	3	2.4	0	2.5291	1.933	-0.08602

22	0.75	2	27.2	0	28.278	58.483	-0.88046
22	1	3	7.78	0	7.3596	6.4154	0.70536
22	1	2	25.8	0	25.413	53.529	-0.38346
22	1.25	3	11.54	0	13.066	13.034	-1.1268
22	1.25	2	20.4	0	19.815	43.586	-0.23369
22	1.5	2	15.26	0	14.912	34.408	-0.22002
22	1.5	3	18.38	0	18.079	20.334	-0.06911
22	2	2	7.22	0	8.2798	21.026	-1.1243
22	2	3	23.2	0	24.386	32.746	-1.0577
22	2	5	224.37	0	181.48	179.8	1.2416
22	2	4	512.04	0	522.13	1084.8	-1.0964
22	2.5	2	4.56	0	4.5818	12.798	-0.14933
22	2.5	3	26.4	0	26.763	39.952	-0.80061
22	3	2	2.36	0	2.5349	7.7869	-0.34906
22	3	3	27.4	0	26.914	42.63	-0.44448
22	3.5	2	1.708	0	1.4025	4.7379	0.59099
22	3.5	3	25.2	0	25.935	42.354	-0.81453
22	4	2	1.288	0	0.77591	2.8827	1.0638
22	4	3	24.2	0	24.436	40.405	-0.49398
22	4	4	614.48	0	629.16	1376	-1.2953
22	4	5	748.09	0	685.89	867.44	-0.1351
22	4.5	2	0.952	0	0.42927	1.754	1.1074
22	4.5	3	23.8	0	22.742	37.627	0.21583
22	5	2	0.514	0	0.2375	1.0672	0.59177
22	5	3	21.8	0	21.025	34.529	0.26145
22	6	3	17.04	0	17.822	28.408	-0.27519
22	8	4	641.5	0	640.13	1421.4	-0.96637
22	8	5	1426.5	0	1385.3	1844.5	-0.59936
22	8.1	3	11.54	0	12.602	18.337	-0.21787
22	10	3	9.48	0	9.3988	12.519	0.90911
22	12	4	651.75	0	640.22	1422.3	-0.74206
22	12	5	1880.6	0	1755.4	2281.5	-0.14088
22	12.05	3	7.58	0	7.053	8.6115	1.5869
22	24	4	651.75	0	640.22	1422.3	-0.74209
22	24	5	2219	0	2222.4	2724.9	-0.3275
22	24.083	3	3.48	0	2.4156	2.3912	2.816
22	36	5	2291.8	0	2437.3	2908.6	-0.58297
22	36.317	3	1.696	0	1.422	1.3602	1.0372
22	48	5	2349.6	0	2573.1	3020.1	-0.67486
22	48.2	3	1.188	0	0.93893	0.85496	0.88385
23	0	1	0	7640	0	0	0
23	0.167	2	0.882	0	0.909	0.57785	-0.06305
23	0.333	2	22.8	0	19.558	17.95	1.0498

23	0.5	3	0.782	0	0.89777	0.20158	-0.32996
23	0.5	2	42	0	49.298	54.783	-1.6733
23	0.75	3	4.62	0	6.6295	1.933	-3.0911
23	0.75	2	63.6	0	67.833	79.709	-1.0335
23	1	3	19.84	0	18.562	6.4154	-0.13761
23	1	2	57	0	63.74	72.957	-0.90795
23	1.25	3	37	0	33.404	13.034	0.32227
23	1.25	2	46	0	52.325	59.405	-0.64467
23	1.5	2	37.6	0	40.287	46.895	-0.05795
23	1.5	3	44.2	0	47.416	20.334	-1.2416
23	2	2	31.6	0	21.795	28.657	3.6784
23	2	3	77.8	0	65.987	32.746	1.8236
23	2	5	535.11	0	439.41	179.8	1.307
23	2	4	1181.5	0	1136.4	1084.8	-0.05572
23	2.5	2	9.24	0	11.157	17.442	-1.1448
23	2.5	3	79.4	0	71.826	39.952	1.428
23	3	2	4.72	0	5.5831	10.613	-1.0539
23	3	3	69.6	0	69.72	42.63	0.48277
23	3.5	2	2.64	0	2.7666	6.4574	-0.34318
23	3.5	3	55.4	0	63.901	42.354	-0.84029
23	4	2	1.42	0	1.3649	3.9289	-0.02383
23	4	3	54.4	0	56.848	40.405	0.044766
23	4	4	1339.6	0	1348	1376	-0.1249
23	4	5	1668.6	0	1631.4	867.44	1.1291
23	4.5	2	1.09	0	0.6721	2.3905	0.76696
23	4.5	3	53.2	0	49.792	37.627	1.1307
23	5	2	0.582	0	0.33065	1.4545	0.46011
23	5	3	45.4	0	43.27	34.529	0.88069
23	6	3	28.6	0	32.412	28.408	-0.88763
23	8	3	15.42	0	18.4	18.721	-1.3217
23	8	4	1360.9	0	1361.6	1421.4	-0.07649
23	8	5	2750.9	0	2846.6	1844.5	0.69168
23	10.067	3	10.98	0	10.796	12.358	0.47673
23	12	3	7.82	0	7.0177	8.6856	1.2897
23	12	4	1360.9	0	1361.6	1422.3	-0.07767
23	12	5	3208.6	0	3256.7	2281.5	0.65769
23	24	4	1360.9	0	1361.6	1422.3	-0.07768
23	24	5	3502.8	0	3618.6	2724.9	0.347
23	24.033	3	2.28	0	1.9312	2.3983	0.84649
23	36	3	1.45	0	1.1168	1.3776	0.81042
23	36	5	3566.8	0	3775.8	2908.6	0.11563
23	48	3	1.046	0	0.66846	0.86159	0.90338
23	48	5	3590.4	0	3868.9	3020.1	-0.04261

24	0	1	0	7640	0	0	0
24	0.167	2	0.516	0	0.2461	0.56691	0.48792
24	0.333	2	10.6	0	10.3	17.61	-0.72073
24	0.5	3	0.494	0	0.27911	0.20158	0.40795
24	0.5	2	44.6	0	39.598	53.745	0.25938
24	0.75	3	1.67	0	3.1076	1.933	-3.2562
24	0.75	2	54.8	0	70.844	78.199	-1.7427
24	1	3	11.62	0	11.197	6.4154	-0.60859
24	1	2	64.4	0	70.402	71.575	-0.38729
24	1.25	3	20.4	0	23.686	13.034	-2.3988
24	1.25	2	50	0	58.384	58.28	-0.8081
24	1.5	3	48	0	37.513	20.334	2.1217
24	1.5	2	62	0	45.642	46.007	2.8809
24	2	2	22.4	0	26.581	28.115	-1.0428
24	2	3	49	0	59.807	32.746	-1.8085
24	2	5	431.29	0	332.44	179.8	1.1918
24	2	4	1082.5	0	1046.5	1084.8	-0.06797
24	2.5	2	15.26	0	15.269	17.112	0.13288
24	2.5	3	71.2	0	70.454	39.952	0.75886
24	3	2	8.24	0	8.7543	10.412	-0.24931
24	3	3	61.2	0	71.866	42.63	-0.55545
24	3.5	2	4.52	0	5.018	6.3351	-0.45739
24	3.5	3	59.4	0	67.98	42.354	-0.23391
24	4	2	3.38	0	2.8763	3.8545	0.94484
24	4	3	79.2	0	61.648	40.405	3.9314
24	4	4	1300	0	1312	1376	-0.22089
24	4	5	1523	0	1503.3	867.44	1.2022
24	4.5	2	1.396	0	1.6486	2.3453	-0.40694
24	4.5	3	47.6	0	54.544	37.627	-0.42389
24	5	2	1.36	0	0.94497	1.4269	0.90139
24	5	3	45.6	0	47.556	34.529	0.28698
24	6	2	1.5	0	0.31046	0.52826	2.534
24	6	3	44.4	0	35.36	28.408	2.9407
24	8	3	16.9	0	19.233	18.721	-1.4626
24	8	4	1333.4	0	1343.8	1421.4	-0.15977
24	8	5	2536.3	0	2778.9	1844.5	0.5283
24	10	3	11.02	0	10.886	12.519	-0.37615
24	12	3	6.22	0	6.6525	8.6856	-1.0653
24	12	4	1344.5	0	1344.2	1422.3	-0.04626
24	12	5	3117.2	0	3175.7	2281.5	0.75782
24	24	3	1.848	0	1.7398	2.4031	0.082858
24	24	4	1350.8	0	1344.2	1422.3	0.020386
24	24	5	3302	0	3493.9	2724.9	0.20263

24	36	3	1.194	0	0.99974	1.3776	0.34948
24	36	5	3350.7	0	3630.4	2908.6	-0.05258
24	48	3	0.822	0	0.59117	0.86159	0.46973
24	48	5	3375.3	0	3710.4	3020.1	-0.20591
25	0	1	0	7640	0	0	0
25	0.167	2	1.41	0	1.2042	0.057111	0.66237
25	0.333	2	22.2	0	20.806	3.3605	1.6494
25	0.5	2	44.2	0	45.223	16.91	0.25792
25	0.75	3	1.502	0	1.2857	0.93495	0.35549
25	0.75	2	51.8	0	55.59	39.07	-0.58175
25	1	3	3.32	0	4.2219	3.9908	-1.9277
25	1	2	52.2	0	50.478	43.716	0.30383
25	1.25	3	8.72	0	8.9914	9.5163	-1.0053
25	1.25	2	45	0	42.05	38.175	0.73315
25	1.5	3	13.76	0	15.039	16.466	-1.7453
25	1.5	2	35.4	0	33.99	30.789	0.61602
25	2	2	20.8	0	21.615	18.967	0.083711
25	2	3	32.8	0	28.125	29.758	0.79894
25	2	5	154.79	0	129.98	145.75	0.000194
25	2	4	1024.9	0	964.58	1034	0.41077
25	2.5	2	13.64	0	13.628	11.552	0.34465
25	2.5	3	39.8	0	39.078	38.384	-0.41853
25	3	2	9.8	0	8.5806	7.0291	1.2738
25	3	3	50.6	0	46.144	42.166	0.72932
25	3.5	2	4.8	0	5.4016	4.2768	-0.46484
25	3.5	3	43.8	0	49.413	42.577	-1.1012
25	4	2	3.68	0	3.4003	2.6022	0.61074
25	4	3	47.4	0	49.73	41.005	-0.16246
25	4	5	882.89	0	829.98	821.1	-0.31022
25	4	4	1229.8	0	1242.1	1369.1	-0.33332
25	4.5	2	2.02	0	2.1404	1.5833	-0.0784
25	4.5	3	48.2	0	48.052	38.405	0.52919
25	5	2	1.524	0	1.3474	0.96333	0.4551
25	5	3	45.8	0	45.186	35.366	0.74654
25	6	2	0.656	0	0.53392	0.35663	0.3116
25	6	3	34.4	0	38.051	29.196	-0.32215
25	8	3	25.4	0	24.915	19.256	0.58918
25	8	4	1269.5	0	1292.5	1421.3	-0.28611
25	8	5	1978.5	0	2047	1822.8	0.010409
25	10	3	21	0	16.126	12.852	3.0291
25	12	3	10.02	0	10.772	8.8911	-0.87782
25	12	4	1274.4	0	1293.8	1422.3	-0.23661
25	12	5	2566.4	0	2582.4	2271.5	0.42486

25	24	3	2.26	0	2.6548	2.4226	-1.0139
25	24	4	1274.4	0	1293.8	1422.3	-0.23657
25	24	5	3024.3	0	3071.7	2722.1	0.37401
25	36	3	0.484	0	1.5016	1.3851	-2.3629
25	36	5	3087.6	0	3262.6	2907	0.07123
25	48	5	3118.4	0	3377	3019.1	-0.11218
26	0	1	0	7640	0	0	0
26	0.167	3	0.354	0	5.02E-07	3.40E-06	0.81708
26	0.333	3	0.74	0	0.000556	0.002483	1.7069
26	0.5	2	4.88	0	7.2548	23.779	-2.734
26	0.75	2	31.6	0	31.657	54.942	-0.98318
26	1	3	2.6	0	2.6097	3.9908	0.41797
26	1	2	67.6	0	53.981	61.476	1.136
26	1.25	3	9.56	0	7.625	9.5163	3.1286
26	1.25	2	74.2	0	59.805	53.683	1.3193
26	1.5	3	14.22	0	15.075	16.466	0.53217
26	1.5	2	49.8	0	54.336	43.297	-0.91125
26	2	3	29.2	0	31.369	29.758	0.1835
26	2	2	30	0	36.859	26.672	-1.4412
26	2	5	102.68	0	123.19	145.75	-0.39787
26	2	4	924.84	0	906.28	1034	-0.68022
26	2.5	2	20.2	0	23.742	16.245	-1.0064
26	2.5	3	38.6	0	43.042	38.384	-0.5851
26	3.017	2	15.74	0	15.003	9.7191	0.55723
26	3.017	3	42.4	0	49.032	42.226	-1.2199
26	3.5	2	9.34	0	9.7691	6.0143	-0.07249
26	3.5	3	46	0	50.603	42.577	-0.92263
26	4	2	6.28	0	6.2658	3.6593	0.24605
26	4	3	51.8	0	49.72	41.005	0.35963
26	4	5	774.22	0	829.85	821.1	-1.0711
26	4	4	1356.9	0	1368	1369.1	-0.2943
26	4.517	2	4.3	0	3.9586	2.1892	0.67745
26	4.517	3	52	0	47.296	38.306	0.91779
26	5	2	2.5	0	2.5776	1.3547	0.020201
26	5	3	43.6	0	44.331	35.366	-0.27589
26	6	2	1.394	0	1.0604	0.5015	0.76117
26	6	3	39.4	0	37.59	29.196	0.3926
26	8	3	28	0	25.824	19.256	0.75427
26	8	4	1459.8	0	1459.4	1421.3	0.097271
26	8	5	2202	0	1987.1	1822.8	0.27378
26	10	3	19.34	0	17.76	12.852	0.74005
26	12	3	13.4	0	12.564	8.8911	0.4397
26	12	4	1467.4	0	1462	1422.3	0.16105

26	12	5	2903.1	0	2545.9	2271.5	0.72275
26	24	3	2.86	0	3.5092	2.4226	-1.3716
26	24	4	1467.4	0	1462.1	1422.3	0.16097
26	24	5	3424.5	0	3134.4	2722.1	0.63888
26	36	3	1.446	0	2.0031	1.3851	-1.2984
26	36	5	3535.7	0	3376.3	2907	0.40298
26	48	3	1.056	0	1.2688	0.86607	-0.56158
26	48	5	3580.8	0	3523.8	3019.1	0.23195
27	0	1	0	7640	0	0	0
27	0.333	3	0.356	0	0.000607	0.002483	0.82024
27	0.5	2	6.8	0	6.5314	23.058	-0.027
27	0.75	3	0.782	0	0.52113	0.93495	0.56248
27	0.75	2	26.6	0	28.473	53.277	-1.095
27	1	3	3.16	0	3.1215	3.9908	-0.09889
27	1	2	52.2	0	48.938	59.613	-0.07718
27	1.25	3	8.3	0	9.5127	9.5163	-1.5351
27	1.25	2	57	0	54.723	52.057	-0.08065
27	1.5	3	20.2	0	19.571	16.466	-0.0906
27	1.5	2	47.8	0	49.87	41.985	-0.52874
27	2	2	27	0	33.085	25.864	-1.3267
27	2	3	48.8	0	43.266	29.758	1.0648
27	2	5	203.01	0	192.2	145.75	-0.23149
27	2	4	918.55	0	891.7	1034	-0.87223
27	2.5	2	18.88	0	20.372	15.752	-0.30832
27	2.5	3	63.6	0	61.059	38.384	0.4359
27	3	2	14.94	0	12.419	9.5852	1.7847
27	3	3	59.4	0	69.396	42.166	-1.2862
27	3.5	2	7.88	0	7.5625	5.832	0.60505
27	3.5	3	72.2	0	70.435	42.577	0.54671
27	4	2	4.4	0	4.6044	3.5484	0.003785
27	4	3	68.4	0	67.115	41.005	0.5168
27	4	4	1299	0	1310.7	1369.1	-0.36155
27	4	5	1368.2	0	1360.8	821.1	0.28651
27	4.5	2	3.14	0	2.8034	2.159	0.76228
27	4.5	3	62.8	0	61.617	38.405	0.50016
27	5	2	1.608	0	1.7068	1.3136	-0.04271
27	5	3	62.2	0	55.298	35.366	1.5331
27	6	2	0.738	0	0.6327	0.48631	0.29067
27	6	3	41	0	42.91	29.196	-0.35152
27	8	3	24.2	0	24.592	19.256	-0.37281
27	8	4	1375.2	0	1376.4	1421.3	0.013986
27	8	5	3161.2	0	2956.7	1822.8	1.2541
27	10	3	14.4	0	14.301	12.852	-0.32057

27	12	3	8.86	0	8.8083	8.8911	-0.36872
27	12	4	1375.2	0	1377.6	1422.3	0.010441
27	12	5	3755.6	0	3502.9	2271.5	1.1898
27	24	3	1.99	0	2.1086	2.4226	-0.4074
27	24	4	1375.2	0	1377.6	1422.3	0.010461
27	24	5	4058.7	0	3932.5	2722.1	0.70836
27	36	3	1.296	0	1.2046	1.3851	0.1099
27	36	5	4122.8	0	4105.8	2907	0.43943
27	48	5	4158.8	0	4207.9	3019.1	0.28498
28	0	1	0	7640	0	0	0
28	0.333	2	3.62	0	5.9359	3.4604	-2.4208
28	0.5	2	25.4	0	20.324	17.413	2.0507
28	0.75	3	2.16	0	1.1685	0.93495	2.5507
28	0.75	2	34.6	0	30.083	40.232	1.3359
28	1	3	4.08	0	3.9233	3.9908	1.0212
28	1	2	26.8	0	26.18	45.017	0.22743
28	1.25	3	9.42	0	7.8662	9.5163	2.6501
28	1.25	2	19.72	0	20.522	39.311	-0.31572
28	1.5	3	8.74	0	12.019	16.466	-1.8271
28	1.5	2	15.78	0	15.867	31.705	-0.10259
28	2	2	9.26	0	9.4588	19.531	-0.23725
28	2	3	15.1	0	18.583	29.758	-1.3998
28	2	5	87.049	0	102.82	145.75	-0.33615
28	2	4	457.41	0	461.67	1034	-0.72968
28	2.5	2	5.84	0	5.6382	11.895	0.14325
28	2.5	3	22.4	0	21.981	38.384	0.37916
28	3	2	2.94	0	3.3608	7.2382	-0.71033
28	3	3	22.4	0	22.932	42.166	-0.24695
28	3.5	2	1.994	0	2.0033	4.4041	-0.05791
28	3.5	3	24.6	0	22.405	42.577	0.84195
28	4	2	1.154	0	1.1941	2.6796	-0.10384
28	4	3	23.4	0	21.099	41.005	0.86271
28	4	5	483.89	0	464.47	821.1	0.30617
28	4	4	558.42	0	573.55	1369.1	-1.4178
28	4.5	2	0.87	0	0.71179	1.6304	0.31672
28	4.5	3	20.8	0	19.444	38.405	0.40555
28	5	2	0.782	0	0.42428	0.99199	0.74722
28	5	3	17.58	0	17.688	35.366	-0.39318
28	6	2	0.676	0	0.15075	0.36723	1.1118
28	6	3	14.34	0	14.348	29.196	-0.37734
28	8	3	8.92	0	9.2596	19.256	-0.7087
28	8	4	582.31	0	589.46	1421.3	-1.2756
28	8	5	959.54	0	948.16	1822.8	-0.56049

28	10	3	6.12	0	6.0965	12.852	-0.28729
28	12	4	594.47	0	589.71	1422.3	-0.99034
28	12	5	1191	0	1156.1	2271.5	-0.70918
28	12.083	3	3.58	0	4.1209	8.7645	-1.1728
28	24	3	1.244	0	1.1487	2.4226	0.13649
28	24	4	604.66	0	589.72	1422.3	-0.74535
28	24	5	1337.3	0	1362.4	2722.1	-1.3496
28	36	3	0.638	0	0.65949	1.3851	-0.09219
28	36	5	1369.9	0	1448.2	2907	-1.714
28	48	3	0.496	0	0.40964	0.86607	0.17019
28	48	5	1399.9	0	1500.1	3019.1	-1.8679
29	0	1	0	7640	0	0	0
29	0.333	2	0.534	0	1.5811	4.474	-2.412
29	0.5	2	11.12	0	10.791	22.513	-1.0118
29	0.75	3	1.218	0	1.1096	0.93495	0.17363
29	0.75	2	39.8	0	34.551	52.016	-0.07135
29	1	3	4.84	0	5.3538	3.9908	-0.88577
29	1	2	47	0	45.796	58.202	-0.50075
29	1.25	3	15.1	0	13.568	9.5163	1.0608
29	1.25	2	43	0	42.074	50.825	-0.18835
29	1.5	3	25	0	23.956	16.466	0.51941
29	1.5	2	32.2	0	33.523	40.992	-0.51078
29	2	2	18.82	0	19.114	25.252	-0.2682
29	2	3	37.2	0	42.413	29.758	-1.0526
29	2	5	227.81	0	217.18	145.75	0.29965
29	2	4	886.94	0	884.04	1034	-0.41787
29	2.5	2	9.94	0	10.685	15.38	-0.61301
29	2.5	3	50.4	0	52.209	38.384	-0.14944
29	3	2	5.64	0	5.9679	9.3583	-0.4331
29	3	3	52	0	54.724	42.166	-0.34759
29	3.5	2	3.42	0	3.3332	5.694	0.08597
29	3.5	3	51.2	0	53.033	42.577	-0.24157
29	4	2	2.2	0	1.8616	3.4645	0.60889
29	4	3	59.4	0	49.312	41.005	2.1622
29	4	5	1127.9	0	1129.4	821.1	0.29438
29	4	4	1145.9	0	1142.9	1369.1	-0.27171
29	4.5	2	1.408	0	1.0397	2.1079	0.73656
29	4.5	3	47.2	0	44.811	38.405	0.57526
29	5	2	0.66	0	0.5807	1.2825	0.16015
29	5	3	41	0	40.195	35.366	0.20462
29	6	3	29.8	0	31.749	29.196	-0.66635
29	8	3	19.38	0	19.572	19.256	-0.17454
29	8	4	1176.8	0	1170.5	1421.3	-0.27104

29	8	5	2339	0	2281.4	1822.8	0.45208
29	10	3	11.7	0	12.411	12.852	-0.63672
29	12	3	8.62	0	8.2637	8.8911	0.30985
29	12	4	1176.8	0	1170.8	1422.3	-0.27545
29	12	5	2920.9	0	2735.6	2271.5	0.69182
29	24	4	1176.8	0	1170.8	1422.3	-0.2755
29	24	5	3286.6	0	3159	2722.1	0.40583
29	24.05	3	2.28	0	2.1898	2.4153	0.14748
29	36	5	3349.8	0	3334.3	2907	0.11663
29	36.05	3	1.278	0	1.2579	1.3823	0.020584
29	48	3	0.896	0	0.77219	0.86607	0.26546
29	48	5	3418.3	0	3439.4	3019.1	0.021089
30	0	1	0	7640	0	0	0
30	0.167	3	0.4	0	1.20E-06	3.40E-06	0.92325
30	0.333	2	1.656	0	2.1885	5.269	-1.3384
30	0.5	3	0.364	0	0.034119	0.065823	0.76355
30	0.5	2	16.34	0	15.779	26.513	-0.74564
30	0.75	3	0.678	0	0.56942	0.93495	0.2855
30	0.75	2	59.4	0	54.835	61.26	-0.11594
30	1	3	2.54	0	2.6175	3.9908	-0.01013
30	1	2	82.6	0	78.742	68.545	0.28962
30	1.25	3	6.54	0	6.3366	9.5163	0.5187
30	1.25	2	78.8	0	78.092	59.856	0.36507
30	1.5	3	10.58	0	10.776	16.466	0.068386
30	1.5	2	67.6	0	66.905	48.276	0.45039
30	2	3	20.2	0	18.34	29.758	1.017
30	2	2	43.4	0	43.814	29.739	0.15062
30	2	5	91.201	0	93.629	145.75	0.077577
30	2	4	1628.6	0	1607.1	1034	0.28899
30	2.5	3	23.4	0	22.644	38.384	0.12324
30	2.5	2	28.6	0	28.063	18.112	0.207
30	3	2	17.82	0	17.954	11.021	-0.09299
30	3	3	26.2	0	24.412	42.166	0.41344
30	3.5	2	11.36	0	11.486	6.7058	-0.17525
30	3.5	3	23.6	0	24.608	42.577	-0.78186
30	4	2	8.54	0	7.3482	4.0801	0.97432
30	4	3	22	0	23.893	41.005	-1.163
30	4	5	508.57	0	489.15	821.1	-0.24843
30	4	4	2308.4	0	2313.4	1369.1	0.67243
30	4.5	2	4.5	0	4.701	2.4825	-0.37738
30	4.5	3	21.2	0	22.681	38.405	-0.98872
30	5	2	2.68	0	3.0075	1.5104	-0.63358
30	5	3	21.6	0	21.229	35.366	-0.10586

30	6	2	1.568	0	1.2309	0.55917	0.61565
30	6	3	18.1	0	18.171	29.196	-0.20022
30	8	2	0.438	0	0.20619	0.076633	0.47707
30	8	3	11.54	0	12.899	19.256	-0.94811
30	8	5	1163.7	0	1108.9	1822.8	-0.54618
30	8	4	2468.3	0	2451.6	1421.3	0.8301
30	10	3	8.86	0	9.2118	12.852	-0.11194
30	12	2	0.744	0	0.005786	0.001439	1.5653
30	12	3	7.62	0	6.7544	8.8911	1.4275
30	12	5	1483.3	0	1428.1	2271.5	-0.64984
30	12	4	2493.1	0	2455.4	1422.3	0.9482
30	24	5	1813.5	0	1797.5	2722.1	-0.78301
30	24	4	2501.8	0	2455.5	1422.3	0.99769
30	24.05	3	2.54	0	2.0739	2.4153	1.2209
30	36	5	1913.9	0	1957.2	2907	-0.96213
30	36.067	3	1.076	0	1.2018	1.3813	-0.12294
30	48	3	0.882	0	0.77834	0.86607	0.34987
30	48	5	1958.2	0	2056.2	3019.1	-1.119
31	0	1	0	7640	0	0	0
31	0.167	2	0.664	0	0.28647	0.096981	0.8168
31	0.333	3	0.432	0	0.006873	0.002483	0.97975
31	0.333	2	13.72	0	11.603	5.7065	2.121
31	0.5	3	0.624	0	0.1483	0.065823	1.0711
31	0.5	2	36.6	0	43.955	28.714	-0.46672
31	0.75	3	1.198	0	1.7098	0.93495	-1.3316
31	0.75	2	54.2	0	79.028	66.345	-2.3358
31	1.017	3	4.98	0	6.9105	4.295	-3.1023
31	1.017	2	84.2	0	78.993	73.918	0.39642
31	1.25	3	14.54	0	14.375	9.5163	-0.90924
31	1.25	2	77.6	0	66.359	64.825	1.1996
31	1.5	3	27	0	23.896	16.466	0.17789
31	1.5	2	60.8	0	51.385	52.284	1.2631
31	2	2	26.8	0	28.516	32.208	-0.73946
31	2	3	40.8	0	41.339	29.758	-0.94898
31	2	5	277.55	0	217.8	145.75	0.55984
31	2	4	1584.6	0	1512.7	1034	1.2095
31	2.5	2	14.48	0	15.33	19.616	-0.74672
31	2.5	3	53.6	0	51.726	38.384	0.073977
31	3	2	6.84	0	8.1803	11.936	-1.3565
31	3	3	57.6	0	55.157	42.166	0.56591
31	3.5	2	4.14	0	4.3573	7.2625	-0.37905
31	3.5	3	55.6	0	54.024	42.577	0.65891
31	4	2	2.78	0	2.32	4.4188	0.80902

31	4	3	51	0	50.488	41.005	0.58476
31	4	5	1254.1	0	1126	821.1	1.1743
31	4	4	1847.8	0	1849.3	1369.1	0.37398
31	4.5	2	1.376	0	1.2351	2.6886	0.30289
31	4.5	3	46	0	45.957	38.405	0.53006
31	5	2	1.098	0	0.65752	1.6358	0.94195
31	5	3	40.6	0	41.218	35.366	0.35996
31	6	2	0.92	0	0.18634	0.60559	1.5672
31	6	3	31.2	0	32.49	29.196	0.03326
31	8	3	19.24	0	19.945	19.256	-0.10975
31	8	4	1876.8	0	1878.6	1421.3	0.24679
31	8	5	2094.3	0	2294.3	1822.8	0.11828
31	10	3	14.68	0	12.612	12.852	1.68
31	12	3	8.82	0	8.3808	8.8911	0.47009
31	12	4	1876.8	0	1878.8	1422.3	0.24315
31	12	5	2576.6	0	2751.9	2271.5	0.24882
31	24	4	1876.8	0	1878.8	1422.3	0.24312
31	24	5	2947.2	0	3176.3	2722.1	0.095965
31	24.017	3	1.914	0	2.2164	2.4201	-0.67761
31	36	3	0.892	0	1.273	1.3851	-0.87876
31	36	5	3018.2	0	3351.7	2907	-0.13888
31	48	3	0.74	0	0.77935	0.86607	-0.11169
31	48	5	3051.5	0	3456.8	3019.1	-0.29006
32	0	1	0	7640	0	0	0
32	0.167	2	1.39	0	1.5868	0.090812	-0.43392
32	0.333	2	40.8	0	36.034	5.3435	1.5329
32	0.5	2	86.4	0	90.532	26.888	0.21314
32	0.75	2	116.4	0	117.73	62.125	0.29875
32	1	3	1.032	0	1.483	3.9908	-1.2135
32	1	2	104.8	0	105.62	69.514	0.41985
32	1.25	3	2.52	0	3.3953	9.5163	-2.0487
32	1.25	2	90.8	0	85.687	60.702	0.90502
32	1.5	3	5.62	0	6.025	16.466	-1.1952
32	1.5	2	68.8	0	67.284	48.958	0.47399
32	2	3	13.38	0	12.42	29.758	-0.08404
32	2	2	51.4	0	40.381	30.159	1.9256
32	2	5	69.964	0	55.462	145.75	0.80621
32	2	4	1937.8	0	1896.6	1034	1.5761
32	2.5	3	18.48	0	18.707	38.384	-0.93502
32	2.5	2	23.8	0	24.049	18.368	-0.48956
32	3	2	12.02	0	14.307	11.177	-1.6906
32	3	3	25	0	23.676	42.166	-0.12973
32	3.5	2	7.32	0	8.5105	6.8006	-1.473

32	3.5	3	25.6	0	26.93	42.577	-1.0431
32	4	2	5.26	0	5.0623	4.1378	-0.17672
32	4	3	29.6	0	28.573	41.005	-0.02472
32	4	5	440.09	0	434.63	821.1	-0.90696
32	4	4	2347.1	0	2363.5	1369.1	0.6307
32	4.5	2	3.08	0	3.0112	2.5176	-0.20479
32	4.5	3	29.2	0	28.926	38.405	-0.15757
32	5	2	1.93	0	1.7911	1.5318	0.03615
32	5	3	28	0	28.354	35.366	-0.26688
32	6	2	0.854	0	0.63374	0.56707	0.35394
32	6	3	24.8	0	25.656	29.196	-0.3189
32	8	3	19.54	0	18.9	19.256	0.47284
32	8	5	1045.1	0	1277.8	1822.8	-1.8761
32	8	4	2439.4	0	2429.3	1421.3	0.60173
32	10	3	13.74	0	13.525	12.852	0.27514
32	12	3	11.08	0	9.8453	8.8911	1.2482
32	12	5	1771.7	0	1741.8	2271.5	-0.15084
32	12	4	2456.4	0	2430.3	1422.3	0.68842
32	24	3	2.94	0	2.8526	2.4226	0.13259
32	24	5	2225.7	0	2261.9	2722.1	-0.1599
32	24	4	2463.4	0	2430.3	1422.3	0.72937
32	36	3	1.606	0	1.6242	1.3851	-0.07001
32	36	5	2338	0	2476.6	2907	-0.38728
32	48	3	0.86	0	1.0499	0.86607	-0.44844
32	48	5	2381.2	0	2608.9	3019.1	-0.5791
33	0	1	0	7640	0	0	0
33	0.167	2	1.648	0	2.0302	0.090492	-0.88574
33	0.333	2	46	0	40.157	5.3247	2.4267
33	0.5	2	86.4	0	83.809	26.793	2.0684
33	0.75	3	1.298	0	1.0692	0.93495	0.759
33	0.75	2	91	0	85.573	61.907	1.1674
33	1	3	3.4	0	3.2712	3.9908	0.87121
33	1	2	76.8	0	68.02	69.269	0.88786
33	1.25	3	6.08	0	6.4809	9.5163	0.40169
33	1.25	2	59.2	0	52.81	60.488	0.26398
33	1.5	3	11.48	0	10.165	16.466	2.2779
33	1.5	2	44.6	0	40.937	48.786	-0.41216
33	2	3	18.78	0	17.193	29.758	1.9419
33	2	5	21.349	0	54.036	145.75	-3.5583
33	2	2	25	0	24.595	30.053	-1.4929
33	2	4	653.29	0	1070.4	1034	-3.4441
33	2.5	2	13.4	0	14.777	18.304	-2.4321
33	2.5	3	20.6	0	22.3	38.384	0.041287

33	3	2	7.56	0	8.8778	11.138	-2.656
33	3	3	23.8	0	25.188	42.166	0.000816
33	3.5	2	4.76	0	5.3338	6.7767	-2.029
33	3.5	3	24.2	0	26.294	42.577	-0.48435
33	4	2	2.88	0	3.2045	4.1232	-1.5633
33	4	3	25.2	0	26.185	41.005	-0.25914
33	4	5	361.5	0	293.73	821.1	1.2684
33	4	4	1357.5	0	1300	1369.1	0.74624
33	4.5	2	1.932	0	1.9253	2.5087	-0.75824
33	4.5	3	26.6	0	25.335	38.405	0.46789
33	5	2	1.434	0	1.1567	1.5264	0.019004
33	5	3	23	0	24.079	35.366	-0.61116
33	6	2	1.056	0	0.41752	0.56507	1.0986
33	6	3	21	0	21.138	29.196	-0.36792
33	8	2	0.456	0	0.054398	0.077442	0.80677
33	8	3	17.18	0	15.709	19.256	0.5513
33	8	5	631.14	0	715.62	1822.8	-1.9503
33	8	4	1402.8	0	1333.9	1421.3	0.35576
33	10	3	13.54	0	11.731	12.852	1.1244
33	12	3	8.52	0	8.9623	8.8911	-0.78469
33	12	5	968.84	0	953.88	2271.5	-1.0976
33	12	4	1417.5	0	1334.4	1422.3	0.48893
33	24	3	2.82	0	3.0918	2.4226	-0.70602
33	24	5	1189.5	0	1261.5	2722.1	-1.5769
33	24	4	1429.6	0	1334.4	1422.3	0.6169
33	36	3	1.6	0	1.8339	1.3851	-0.62453
33	36	5	1354.8	0	1402.8	2907	-1.3464
33	48	3	1.09	0	1.223	0.86607	-0.38691
33	48	5	1393.4	0	1492.9	3019.1	-1.5371
34	0	1	0	7640	0	0	0
34	0.333	2	2.52	0	3.5854	4.8007	-1.8172
34	0.5	3	0.564	0	0.13059	0.065823	1.0284
34	0.5	2	23.4	0	19.442	24.157	1.1949
34	0.75	3	2.18	0	1.5464	0.93495	1.592
34	0.75	2	47	0	51.633	55.814	-0.64632
34	1	3	5.02	0	5.5941	3.9908	-0.4334
34	1	2	68.2	0	67.17	62.452	0.24517
34	1.25	3	11.36	0	11.623	9.5163	0.18248
34	1.25	2	68.2	0	67.281	54.536	0.32457
34	1.5	3	19.58	0	18.086	16.466	1.1216
34	1.5	2	53.8	0	60.832	43.985	-0.55117
34	2	3	28.4	0	28.74	29.758	-0.06505
34	2	2	39.2	0	44.752	27.095	-0.49365

34	2	5	143.28	0	133.39	145.75	0.71032
34	2	4	1197.6	0	1221.5	1034	-1.0483
34	2.5	2	28.4	0	31.589	16.502	-0.29808
34	2.5	3	35.4	0	35.204	38.384	-0.01506
34	3	2	23	0	22.092	10.042	0.7027
34	3	3	38.4	0	38.303	42.166	-0.07675
34	3.5	2	18.76	0	15.417	6.1097	1.8818
34	3.5	3	39.8	0	39.117	42.577	0.098415
34	4	2	13.44	0	10.754	3.7174	1.961
34	4	3	38.4	0	38.468	41.005	-0.04804
34	4	5	749.94	0	656.91	821.1	0.4165
34	4	4	1963.8	0	1905	1369.1	0.53336
34	4.5	2	8.24	0	7.5005	2.2618	0.74755
34	4.5	3	37.4	0	36.929	38.405	0.16363
34	5	2	4.4	0	5.2311	1.3762	-0.98306
34	5	3	33.2	0	34.886	35.366	-0.39049
34	6	2	1.742	0	2.5444	0.50946	-1.4388
34	6	3	31	0	30.23	29.196	0.50076
34	8	2	0.428	0	0.60199	0.069821	-0.40234
34	8	3	20.8	0	21.562	19.256	0.12356
34	8	5	1655.7	0	1517.8	1822.8	0.15264
34	8	4	2131.2	0	2105.7	1421.3	0.84188
34	10	3	15.14	0	15.228	12.852	0.5804
34	12	3	11.42	0	10.975	8.8911	1.1009
34	12	5	1865.4	0	1961.4	2271.5	-0.65797
34	12	4	2135.7	0	2117	1422.3	0.86112
34	24	3	3.64	0	3.1618	2.4226	1.366
34	24	4	2135.7	0	2117.6	1422.3	0.86262
34	24	5	2359	0	2448.8	2722.1	-0.29468
34	36	5	2468.2	0	2651.4	2907	-0.43783
34	36.083	3	2.04	0	1.8028	1.3804	0.79731
34	48	5	2532.9	0	2775.7	3019.1	-0.51865
34	48.083	3	1.176	0	1.1519	0.86329	0.25979
35	0	1	0	7640	0	0	0
35	0.333	2	1.498	0	2.2198	4.0218	-1.6182
35	0.5	3	0.43	0	0.12381	0.065823	0.73525
35	0.5	2	13.44	0	13.429	20.237	-0.85516
35	0.75	3	2.52	0	1.787	0.93495	1.9044
35	0.75	2	41.4	0	37.727	46.759	-0.21282
35	1	3	8.1	0	7.3647	3.9908	1.7018
35	1	2	49	0	46.845	52.32	-0.40383
35	1.25	3	15.6	0	16.475	9.5163	0.3535
35	1.25	2	43.2	0	42.684	45.688	-0.47709

35	1.5	3	23	0	26.485	16.466	-0.7091
35	1.5	2	34.8	0	34.953	36.849	-0.44405
35	2	2	20.4	0	21.826	22.7	-0.60678
35	2	3	39.8	0	41.941	29.758	-0.47835
35	2	5	264	0	270.04	145.75	0.14618
35	2	4	1116.7	0	1074.4	1034	-0.16224
35	2.5	2	13.16	0	13.462	13.825	-0.07475
35	2.5	3	46.2	0	49.366	38.384	-0.91805
35	3	2	8.06	0	8.2986	8.4125	0.003352
35	3	3	53.8	0	51.174	42.166	0.16964
35	3.5	2	5.06	0	5.1153	5.1185	0.16884
35	3.5	3	51.6	0	49.775	42.577	0.026962
35	4	2	3.28	0	3.1531	3.1143	0.4212
35	4	3	49.8	0	46.717	41.005	0.37893
35	4	5	1333.2	0	1249.6	821.1	0.42383
35	4	4	1458	0	1460.1	1369.1	-0.06801
35	4.5	2	2.5	0	1.9436	1.8949	1.2181
35	4.5	3	47	0	42.921	38.405	0.74477
35	5	2	1.282	0	1.198	1.1529	0.31211
35	5	3	39.2	0	38.917	35.366	-0.07929
35	6	2	0.652	0	0.45521	0.42681	0.49133
35	6	3	30.4	0	31.321	29.196	-0.31658
35	8	3	20.2	0	19.81	19.256	0.37115
35	8	4	1519.2	0	1523.8	1421.3	0.10382
35	8	5	2788.5	0	2531.8	1822.8	0.85639
35	10	3	11.84	0	12.76	12.852	-0.43521
35	12	3	8.4	0	8.5828	8.8911	0.09305
35	12	4	1519.2	0	1525.2	1422.3	0.099549
35	12	5	3349.9	0	3061.3	2271.5	0.88227
35	24	3	2.66	0	2.2877	2.4226	0.89153
35	24	4	1519.2	0	1525.2	1422.3	0.099548
35	24	5	3761.1	0	3564.1	2722.1	0.65478
35	36	5	3807.8	0	3771.3	2907	0.33969
35	36.633	3	1.544	0	1.2778	1.3503	0.6632
35	48	3	1.096	0	0.80737	0.86607	0.70642
35	48	5	3841.7	0	3895.9	3019.1	0.17701
36	0	1	0	7640	0	0	0
36	0.5	2	3.04	0	2.863	20.905	0.68333
36	0.75	2	14.42	0	13.418	48.301	0.81941
36	1	2	22	0	25.373	54.045	-1.3526
36	1.25	3	2.5	0	1.2202	9.5163	2.9925
36	1.25	2	33.4	0	31.505	47.194	-0.31263
36	1.5	3	2.8	0	2.9948	16.466	-0.16804

36	1.5	2	29.8	0	31.631	38.064	-1.3074
36	2	3	7.22	0	9.276	29.758	-2.0586
36	2	2	24.2	0	23.854	23.448	-0.61669
36	2	5	28.649	0	41.26	145.75	-3.0653
36	2	4	853.76	0	848.71	1034	-0.78657
36	2.5	2	17.2	0	15.264	14.281	0.4554
36	2.5	3	18.5	0	17.54	38.384	0.19304
36	3	2	8.52	0	9.1378	8.6898	-0.74311
36	3	3	26.8	0	25.309	42.166	0.042555
36	3.5	2	4.78	0	5.3029	5.2873	-0.75484
36	3.5	3	31.8	0	31.016	42.577	-0.34069
36	4	2	3.06	0	3.0299	3.217	-0.01613
36	4	3	37.4	0	34.223	41.005	0.40152
36	4	5	724.63	0	582.51	821.1	-0.56985
36	4	4	1362.8	0	1344.5	1369.1	0.11509
36	4.5	2	1.734	0	1.7173	1.9574	0.00531
36	4.5	3	34.6	0	35.207	38.405	-0.62611
36	5	2	1.3	0	0.9692	1.1909	0.66708
36	5	3	33	0	34.531	35.366	-0.80027
36	6	2	0.704	0	0.30694	0.44088	0.83871
36	6	3	28.6	0	30.413	29.196	-0.78482
36	8	3	20	0	20.235	19.256	-0.11046
36	8	4	1408.5	0	1405.8	1421.3	-0.04095
36	8	5	2029.6	0	1912	1822.8	-0.03788
36	10	3	12.98	0	12.916	12.852	0.14522
36	12	3	8.72	0	8.459	8.8911	0.42755
36	12	4	1415.8	0	1406.4	1422.3	0.023606
36	12	5	2635.9	0	2515.6	2271.5	0.39142
36	24	3	2.26	0	1.9079	2.4226	0.84278
36	24	4	1415.8	0	1406.4	1422.3	0.023472
36	24	5	3132.7	0	3033.8	2722.1	0.41417
36	36	3	0.776	0	1.065	1.3851	-0.59399
36	36	5	3286.2	0	3225	2907	0.3013
36	48	3	0.9	0	0.6555	0.86607	0.59697
36	48	5	3332.8	0	3339	3019.1	0.13808
37	0	1	0	7640	0	0	0
37	0.167	2	2.94	0	2.6791	0.06425	1.354
37	0.333	2	33.8	0	37.905	3.7805	1.812
37	0.5	3	1.148	0	0.44291	0.065823	1.7775
37	0.5	2	76.8	0	65.407	19.023	2.3331
37	0.75	3	4.08	0	2.9174	0.93495	2.9244
37	0.75	2	72.8	0	62.007	43.954	0.8024
37	1	3	5.9	0	7.8173	3.9908	-1.1513

37	1	2	57.6	0	49.82	49.181	0.20773
37	1.25	3	12.44	0	14.046	9.5163	0.002032
37	1.25	2	41.4	0	39.483	42.947	-0.86104
37	1.5	3	24.4	0	20.398	16.466	3.0455
37	1.5	2	31.8	0	31.261	34.638	-1.2702
37	2	2	17.12	0	19.593	21.338	-2.4511
37	2	3	32.4	0	30.755	29.758	1.3477
37	2	5	114.07	0	172.26	145.75	-0.72988
37	2	4	602.2	0	1069	1034	-4.1811
37	2.5	2	9.44	0	12.28	12.996	-3.072
37	2.5	3	36.4	0	36.801	38.384	0.35658
37	3	2	5.74	0	7.6967	7.9078	-2.9011
37	3	3	35.4	0	39.218	42.166	-0.83142
37	3.5	2	4.24	0	4.824	4.8114	-1.6407
37	3.5	3	37	0	39.203	42.577	-0.65521
37	4	2	3.46	0	3.0235	2.9275	0.025426
37	4	3	37.8	0	37.745	41.005	-0.24628
37	4	5	707.34	0	769.2	821.1	-0.56316
37	4	4	1183.9	0	1322	1369.1	-1.2451
37	4.5	2	1.982	0	1.895	1.7812	-0.32913
37	4.5	3	36.8	0	35.518	38.405	-0.01535
37	5	2	1.804	0	1.1877	1.0837	0.88996
37	5	3	35	0	32.948	35.366	0.17646
37	6	2	1.072	0	0.46657	0.4012	1.105
37	6	3	31.4	0	27.698	29.196	0.85394
37	7	2	0.498	0	0.18328	0.14853	0.58867
37	7	3	18.6	0	22.97	23.741	-2.3852
37	8	4	1501	0	1367	1421.3	1.1733
37	8	5	1853.1	0	1658.5	1822.8	0.27173
37	10	3	13.12	0	13.162	12.852	-0.26645
37	12	3	9.16	0	9.4051	8.8911	-0.35917
37	12	4	1517	0	1368.1	1422.3	1.3074
37	12	5	2326	0	2087.6	2271.5	0.26485
37	24	3	3.04	0	2.7462	2.4226	0.61827
37	24	4	1524.7	0	1368.1	1422.3	1.3866
37	24	5	2759.8	0	2554.2	2722.1	0.17108
37	36	5	2865.4	0	2751.5	2907	-0.04081
37	36.183	3	1.38	0	1.5696	1.3749	-0.38011
37	48	3	0.942	0	1.0045	0.86607	-0.11474
37	48	5	2906.7	0	2872.4	3019.1	-0.21189
38	0	1	0	7640	0	0	0
38	0.333	2	1.142	0	0.80602	3.8479	0.65262
38	0.5	2	7.58	0	7.3478	19.362	-0.02137

38	0.75	2	32.2	0	34.82	44.737	-0.95131
38	1	3	0.41	0	0.45922	3.9908	-0.13977
38	1	2	71.8	0	63.817	50.057	0.97689
38	1.25	3	1.92	0	1.6023	9.5163	0.60665
38	1.25	2	77	0	74.728	43.712	0.73524
38	1.5	3	2.62	0	3.7494	16.466	-2.1707
38	1.5	2	77.6	0	70.332	35.255	1.4752
38	2	3	9.82	0	10.464	29.758	-0.93483
38	2	5	39.337	0	41.437	145.75	-1.4293
38	2	2	50.8	0	48.794	21.718	0.83273
38	2	4	1213.8	0	1192.6	1034	-0.22683
38	2.5	3	21.8	0	17.975	38.384	1.7127
38	2.5	2	32	0	31.256	13.227	0.40542
38	3	2	19.04	0	19.833	8.0486	-0.25998
38	3	3	25.2	0	24	42.166	0.10857
38	3.5	2	12.36	0	12.575	4.8971	-0.18493
38	3.5	3	27	0	27.763	42.577	-0.63217
38	4	2	7.6	0	7.972	2.9796	-0.41811
38	4	3	29.2	0	29.445	41.005	-0.38507
38	4	5	514.36	0	466.27	821.1	-0.72534
38	4	4	1821.3	0	1835.2	1369.1	0.34027
38	4.5	2	5.46	0	5.054	1.8129	0.39164
38	4.5	3	27.4	0	29.566	38.405	-0.99211
38	5	2	3.1	0	3.2041	1.1031	-0.25246
38	5	3	26.8	0	28.655	35.366	-0.85443
38	6	2	1.624	0	1.2878	0.40835	0.61963
38	6	3	25.8	0	25.306	29.196	0.092961
38	8	2	0.542	0	0.20802	0.055963	0.69616
38	8	3	17.68	0	17.857	19.256	-0.05726
38	8	5	1491.4	0	1402.4	1822.8	-0.21637
38	8	4	1956.7	0	1956	1421.3	0.51092
38	10	3	12.3	0	12.314	12.852	0.11926
38	12	3	9.2	0	8.6707	8.8911	0.72516
38	12	5	1945.1	0	1878.1	2271.5	-0.12046
38	12	4	1971.2	0	1959.2	1422.3	0.59029
38	24	3	2.64	0	2.3015	2.4226	0.79174
38	24	4	1981.3	0	1959.3	1422.3	0.66263
38	24	5	2364.5	0	2366.8	2722.1	-0.16703
38	36	3	0.95	0	1.2964	1.3851	-0.70987
38	36	5	2449.8	0	2560.1	2907	-0.42225
38	48	3	1.022	0	0.82228	0.86607	0.49439
38	48	5	2497.1	0	2677.4	3019.1	-0.57182
39	0	1	0	7640	0	0	0

39	0.167	2	0.964	0	0.98085	0.074927	0.003417
39	0.333	2	25.2	0	24.145	4.4088	1.0052
39	0.5	3	0.426	0	0.083698	0.065823	0.78732
39	0.5	2	67.2	0	59.711	22.185	1.4597
39	0.75	3	1.156	0	0.78806	0.93495	0.79524
39	0.75	2	76.6	0	70.795	51.258	0.21943
39	1	3	2.54	0	2.7137	3.9908	-0.5283
39	1	2	65.6	0	60.965	57.354	0.009644
39	1.25	3	4.38	0	5.9073	9.5163	-2.5733
39	1.25	2	51	0	50.482	50.084	-0.38267
39	1.5	3	7.52	0	10.025	16.466	-3.0544
39	1.5	2	42.8	0	41.658	40.394	-0.11771
39	2	3	21.2	0	19.237	29.758	0.10877
39	2	2	26	0	28.352	24.883	-0.66625
39	2	5	102.5	0	96.757	145.75	-0.9869
39	2	4	1419.3	0	1447	1034	-0.03652
39	2.6	2	15.72	0	17.866	13.722	-0.63684
39	2.6	3	34.8	0	28.824	39.487	1.345
39	3	2	10.8	0	13.132	9.2219	-0.87691
39	3	3	32.8	0	33.265	42.166	-0.70461
39	3.5	2	6.42	0	8.9372	5.611	-1.4087
39	3.5	3	42.4	0	36.465	42.577	1.3644
39	4	2	5.7	0	6.0824	3.414	0.2202
39	4	3	37.6	0	37.427	41.005	-0.01319
39	4	5	741.81	0	660.22	821.1	-0.12096
39	4	4	1926.7	0	1938	1369.1	0.17449
39	4.5	2	4.82	0	4.1395	2.0772	1.5653
39	4.5	3	36.6	0	36.722	38.405	0.089894
39	5	2	3.18	0	2.8172	1.2638	1.1734
39	5	3	34.6	0	34.906	35.366	0.16124
39	6	2	2.94	0	1.3049	0.46788	3.6435
39	6	3	28.4	0	29.653	29.196	-0.07714
39	8	2	1.212	0	0.27993	0.064121	2.1002
39	8	3	18.12	0	18.97	19.256	-0.24833
39	8	5	1703.3	0	1705.7	1822.8	0.062042
39	8	4	2084.1	0	2065.9	1421.3	0.58947
39	10	2	0.598	0	0.060055	0.008788	1.1779
39	10	3	11.36	0	11.62	12.852	-0.2646
39	12	3	7.18	0	7.2765	8.8911	-0.32308
39	12	5	2101.3	0	2138.4	2271.5	0.065686
39	12	4	2120.9	0	2071.8	1422.3	0.82481
39	24	3	1.944	0	1.5534	2.4226	0.69816
39	24	4	2142.5	0	2072	1422.3	0.9727

39	24	5	2374.8	0	2475.1	2722.1	-0.31859
39	36	3	1.08	0	0.87385	1.3851	0.37794
39	36	5	2451.2	0	2599.5	2907	-0.54911
39	48	3	0.874	0	0.52653	0.86607	0.73789
39	48	5	2483.7	0	2672.9	3019.1	-0.71504
40	0	1	0	7640	0	0	0
40	0.333	2	6.24	0	8.7156	3.1636	-2.5068
40	0.5	2	39.4	0	33.001	15.919	0.59146
40	0.75	3	7.96	0	6.9242	0.93495	1.9844
40	0.75	2	60.8	0	53.701	36.781	0.59032
40	1	3	17.88	0	19.56	3.9908	0.047561
40	1	2	48.6	0	48.112	41.156	-0.09444
40	1.25	3	35	0	33.322	9.5163	1.2193
40	1.25	2	38	0	37.533	35.939	0.027603
40	1.5	2	28.6	0	28.621	28.986	0.022214
40	1.5	3	33.2	0	44.387	16.466	-2.1436
40	2	2	14.86	0	16.547	17.856	-0.55161
40	2	3	51.2	0	56.619	29.758	-0.86741
40	2	5	533.06	0	494.2	145.75	1.1045
40	2	4	1189	0	1149.9	1034	0.14592
40	2.5	2	9.2	0	9.5638	10.875	0.040133
40	2.5	3	59.8	0	59.69	38.384	0.054504
40	3	2	5.18	0	5.5276	6.6174	-0.05342
40	3	3	78.8	0	57.903	42.166	3.7612
40	3.5	2	2.86	0	3.1948	4.0263	-0.21258
40	3.5	3	46	0	53.801	42.577	-1.3596
40	4	2	2.4	0	1.8465	2.4498	1.2917
40	4	3	48.6	0	48.789	41.005	0.1608
40	4	4	1393.3	0	1413.9	1369.1	-0.28398
40	4	5	1906	0	1696.8	821.1	1.3906
40	4.5	2	1.502	0	1.0672	1.4905	1.0671
40	4.5	3	39	0	43.618	38.405	-0.81144
40	5	2	1.212	0	0.61684	0.9069	1.372
40	5	3	28.8	0	38.672	35.366	-2.2745
40	6	2	0.754	0	0.20606	0.33573	1.2174
40	6	3	32.4	0	30.047	29.196	1.2126
40	8	3	21.2	0	18.105	19.256	2.1407
40	8	4	1447.2	0	1446.6	1421.3	-0.01006
40	8	5	3260.7	0	3031.8	1822.8	1.1076
40	10	3	11.5	0	11.301	12.852	0.50587
40	12	3	6.78	0	7.4621	8.8911	-0.58566
40	12	4	1447.2	0	1447	1422.3	-0.0124
40	12	5	3700.4	0	3535.8	2271.5	0.90508

40	24	3	2.2	0	2.0563	2.4226	0.33412
40	24	4	1447.2	0	1447	1422.3	-0.01242
40	24	5	4007.5	0	4004.9	2722.1	0.57602
40	36	3	1.112	0	1.1869	1.3851	-0.15066
40	36	5	4071.4	0	4205.3	2907	0.34394
40	48	3	0.832	0	0.72091	0.86607	0.26043
40	48	5	4101.2	0	4325.1	3019.1	0.20032
41	0	1	0	7640	0	0	0
41	0.333	2	1.036	0	0.30034	4.7554	1.5651
41	0.5	2	3.24	0	2.7795	23.929	0.81191
41	0.75	3	0.586	0	0.085395	0.93495	1.1541
41	0.75	2	13.28	0	14.094	55.288	-0.47031
41	1	3	0.886	0	0.59848	3.9908	0.64528
41	1	2	29.6	0	29.018	61.863	-0.10586
41	1.25	3	1.582	0	2.1469	9.5163	-1.2301
41	1.25	2	36	0	39.393	54.021	-1.0181
41	1.5	3	4.1	0	5.1979	16.466	-1.7945
41	1.5	2	44.2	0	43.294	43.57	-0.24157
41	2	3	19.52	0	15.587	29.758	2.2274
41	2	2	40.6	0	38.872	26.84	0.012531
41	2	5	50.219	0	50.422	145.75	-0.6356
41	2	4	778.39	0	777.8	1034	-1.3451
41	2.5	3	27.2	0	28.494	38.384	-0.68183
41	2.5	2	27.4	0	29.135	16.347	-0.67639
41	3.133	2	20.4	0	18.002	8.7154	0.78777
41	3.133	3	39.8	0	42.27	42.54	-0.65785
41	3.5	2	13.84	0	13.167	6.0521	0.17371
41	3.5	3	47.4	0	47.489	42.577	0.020514
41	4	2	8.92	0	8.3884	3.6823	0.22772
41	4	3	52.6	0	51.196	41.005	0.43413
41	4	5	676.81	0	653.38	821.1	-0.71565
41	4	4	1488.3	0	1475.4	1369.1	-0.10547
41	4.5	2	5.24	0	5.2387	2.2405	-0.20913
41	4.5	3	51	0	51.684	38.405	0.091377
41	5	2	2.68	0	3.2268	1.3632	-1.0444
41	5	3	46.8	0	49.939	35.366	-0.3853
41	6	2	1.128	0	1.1917	0.50466	-0.23876
41	6	3	47.2	0	43.094	29.196	1.196
41	8	3	30.2	0	28.145	19.256	0.72434
41	8	4	1613	0	1613.8	1421.3	0.22377
41	8	5	1952.5	0	2009.3	1822.8	-0.23872
41	10	3	18.22	0	17.832	12.852	-0.00029
41	12	4	1630.4	0	1616.2	1422.3	0.36231

41	12	5	2786.1	0	2604.4	2271.5	0.74719
41	12.05	3	10.4	0	11.514	8.8145	-1.2346
41	24	3	2.76	0	2.6429	2.4226	0.080123
41	24	4	1641.4	0	1616.2	1422.3	0.45916
41	24	5	3194.7	0	3112.7	2722.1	0.44455
41	36	3	1.45	0	1.4807	1.3851	-0.15357
41	36	5	3288.1	0	3302.1	2907	0.19089
41	48	3	0.956	0	0.90889	0.86607	0.0493
42	0	1	0	7640	0	0	0
42	0.333	2	0.938	0	1.9878	4.1774	-2.341
42	0.5	2	14.54	0	14.186	21.02	-1.0015
42	0.75	3	0.522	0	0.070855	0.93495	1.0353
42	0.75	2	54.8	0	48.517	48.568	0.092775
42	1	3	0.94	0	0.42474	3.9908	1.1617
42	1	2	73.8	0	68.61	54.344	0.46708
42	1.25	3	1.65	0	1.3423	9.5163	0.63266
42	1.25	2	69	0	67.18	47.455	0.55403
42	1.5	3	3.32	0	2.9431	16.466	0.64064
42	1.5	2	54.4	0	57.003	38.274	0.12636
42	2	3	5.8	0	7.7481	29.758	-2.4618
42	2	2	37.4	0	36.832	23.577	0.46634
42	2	5	37.639	0	32.812	145.75	0.20921
42	2	4	1545.9	0	1451.3	1034	0.80795
42	2.5	3	13.26	0	13.274	38.384	-0.38008
42	2.5	2	22.8	0	23.329	14.36	0.030826
42	3	2	14.88	0	14.763	8.7378	0.13984
42	3	3	18.64	0	18.127	42.166	-0.2014
42	3.5	2	9.9	0	9.3422	5.3165	0.41913
42	3.5	3	21.6	0	21.658	42.577	-0.58145
42	4	2	6.36	0	5.9118	3.2348	0.44
42	4	3	22.6	0	23.778	41.005	-1.0871
42	4	5	376.9	0	367.11	821.1	-1.3983
42	4	4	2070.3	0	2062.7	1369.1	0.66219
42	4.5	2	3.62	0	3.741	1.9682	-0.24245
42	4.5	3	25.6	0	24.686	38.405	-0.21214
42	5	2	2.46	0	2.3673	1.1975	0.10028
42	5	3	23.2	0	24.672	35.366	-1.167
42	6	2	0.836	0	0.94797	0.44332	-0.26657
42	6	3	22.8	0	22.971	29.196	-0.54113
42	8	3	18.26	0	17.555	19.256	0.21404
42	8	5	1229.3	0	1228.4	1822.8	-1.1578
42	8	4	2153.1	0	2176.5	1421.3	0.53568
42	10	3	12.84	0	12.874	12.852	0.053146

42	12	3	10.5	0	9.543	8.8911	1.2008
42	12	5	1787.3	0	1735.1	2271.5	-0.51038
42	12	4	2159.6	0	2179.4	1422.3	0.55984
42	24	3	3.3	0	2.8673	2.4226	1.2111
42	24	4	2159.6	0	2179.5	1422.3	0.55933
42	24	5	2371	0	2328.5	2722.1	-0.10965
42	36	3	1.482	0	1.638	1.3851	-0.08422
42	36	5	2555.9	0	2577.1	2907	-0.13399
42	48	3	1.15	0	1.0722	0.86607	0.3653
42	48	5	2622.3	0	2731.5	3019.1	-0.26726
43	0	1	0	7640	0	0	0
43	0.167	2	0.792	0	0.57287	0.076261	0.48652
43	0.333	3	0.35	0	0.12719	0.002483	0.52872
43	0.333	2	14.12	0	14.127	4.4873	0.029148
43	0.5	3	1.706	0	1.7068	0.065823	0.11646
43	0.5	2	38.2	0	37.435	22.58	-0.38879
43	0.75	3	10.78	0	10.995	0.93495	0.1908
43	0.75	2	46.8	0	50.033	52.171	-1.2853
43	1	3	29.4	0	26.543	3.9908	1.5482
43	1	2	42.2	0	44.252	58.375	-0.85352
43	1.3	2	33.2	0	32.672	49.007	-0.09715
43	1.3	3	42	0	44.704	10.837	-0.26137
43	1.5	2	28	0	25.77	41.113	0.50386
43	1.5	3	54.8	0	53.889	16.466	0.4609
43	2	2	14.94	0	13.669	25.326	0.51609
43	2	3	62.4	0	66.021	29.758	-0.36492
43	2	5	574.12	0	526	145.75	1.345
43	2	4	922.12	0	946.11	1034	-0.73639
43	2.5	2	7.22	0	7.1242	15.425	-0.13417
43	2.5	3	71.6	0	67.654	38.384	0.76771
43	3	2	3.28	0	3.7	9.3861	-0.83564
43	3	3	63.4	0	64.136	42.166	0.043416
43	3.5	2	1.742	0	1.9202	5.7109	-0.499
43	3.5	3	54.4	0	58.516	42.577	-0.55705
43	4	2	1.124	0	0.99643	3.4747	0.1508
43	4	3	54.4	0	52.329	41.005	0.57995
43	4	4	1119.4	0	1110.7	1369.1	-0.28979
43	4	5	1925	0	1673.6	821.1	1.7264
43	4.5	2	0.716	0	0.51704	2.1142	0.34999
43	4.5	3	46	0	46.302	38.405	0.12267
43	5	2	0.494	0	0.26829	1.2863	0.43702
43	5	3	41	0	40.748	35.366	0.26878
43	6	3	34.4	0	31.394	29.196	1.2081

43	8	3	18.4	0	18.866	19.256	0.001183
43	8	4	1137.2	0	1123.5	1421.3	-0.26657
43	8	5	2973	0	2877.2	1822.8	0.82705
43	10	3	12.26	0	11.832	12.852	0.56377
43	12	3	8.22	0	7.8695	8.8911	0.56596
43	12	4	1137.2	0	1123.6	1422.3	-0.26798
43	12	5	3406.6	0	3329.4	2271.5	0.73324
43	24	4	1137.2	0	1123.6	1422.3	-0.26799
43	24	5	3599	0	3760.1	2722.1	0.24364
43	24.15	3	2.08	0	2.215	2.4009	-0.23923
43	36	3	1.162	0	1.2928	1.3851	-0.26792
43	36	5	3677.6	0	3947.2	2907	0.060033
43	48	3	0.698	0	0.78554	0.86607	-0.18435
44	0	1	0	7640	0	0	0
44	0.5	2	0.724	0	0.12688	21.556	1.2766
44	0.75	2	2.88	0	1.466	49.806	2.8612
44	1	3	0.69	0	0.28716	3.9908	0.90936
44	1	2	4.8	0	5.9327	55.729	-1.2777
44	1.25	3	1.266	0	1.4324	9.5163	-0.45645
44	1.25	2	9.6	0	13.596	48.665	-2.6234
44	1.5	3	2.5	0	4.4627	16.466	-3.4906
44	1.5	2	15.86	0	21.879	39.25	-2.7738
44	2	3	18.36	0	18.359	29.758	-0.6896
44	2	2	40	0	29.754	24.179	2.0022
44	2	5	52.585	0	51.134	145.75	-1.2964
44	2	4	386.22	0	366.67	1034	-2.6327
44	2.5	2	24.6	0	24.458	14.726	-0.13351
44	2.5	3	46.6	0	38.468	38.384	1.5698
44	3	2	12.66	0	15.265	8.9606	-1.2063
44	3	3	61	0	55.327	42.166	0.73693
44	3.5	2	7.62	0	8.1973	5.452	-0.34682
44	3.5	3	69.2	0	64.181	42.577	0.73755
44	4	2	4.04	0	4.0715	3.3172	0.13445
44	4	3	65.6	0	65.939	41.005	0.059339
44	4	4	907.49	0	923.98	1369.1	-0.86532
44	4	5	1083.3	0	885.08	821.1	-0.07296
44	4.5	2	2.9	0	1.9482	2.0183	1.9243
44	4.5	3	60	0	63.379	38.405	-0.31205
44	5	2	1.138	0	0.91725	1.228	0.56072
44	5	3	50.6	0	58.803	35.366	-1.0987
44	6	2	0.494	0	0.20027	0.45462	0.65984
44	6	3	47.2	0	48.395	29.196	0.25113
44	8	3	28.6	0	31.643	19.256	-0.18441

44	8	4	960.98	0	970.65	1421.3	-0.56717
44	8	5	2576.7	0	2501.2	1822.8	0.206
44	10	3	19.9	0	21.098	12.852	0.38614
44	12	3	14.82	0	14.589	8.8911	1.1522
44	12	4	963.89	0	970.76	1422.3	-0.52788
44	12	5	3200.8	0	3220.9	2271.5	0.47788
44	24	3	4.94	0	3.8583	2.4226	2.4142
44	24	4	963.89	0	970.76	1422.3	-0.52789
44	24	5	3955.2	0	3936	2722.1	0.97616
44	36	5	4156	0	4222	2907	0.94005
44	36.05	3	2.3	0	2.1839	1.3823	0.55823
44	48.033	3	1.632	0	1.3719	0.86496	0.79298
45	0	1	0	7640	0	0	0
45	0.167	2	1.942	0	2.4002	0.099227	-0.94486
45	0.333	3	0.628	0	0.063715	0.002483	1.3051
45	0.333	2	36.4	0	32.275	5.8387	1.3701
45	0.5	3	1.434	0	0.7453	0.065823	1.6042
45	0.5	2	49.2	0	51.148	29.38	-0.57601
45	0.75	3	4.88	0	4.4492	0.93495	0.81548
45	0.75	2	44.4	0	42.392	67.882	-0.61251
45	1	3	8.88	0	10.846	3.9908	-1.6956
45	1	2	32.8	0	30.282	75.955	-0.37156
45	1.25	3	18.46	0	17.882	9.5163	0.23547
45	1.25	2	21.4	0	21.452	66.327	-0.93306
45	1.5	2	14.18	0	15.191	53.495	-1.2991
45	1.5	3	24.2	0	24.044	16.466	-0.09287
45	2	5	277.89	0	238.5	145.75	1.3246
45	2	4	807.74	0	811.97	1034	0.19105
45	2.017	2	6.62	0	7.4415	32.405	-1.3139
45	2.017	3	30.8	0	32	30.139	-0.58527
45	2.5	2	3.56	0	3.8204	20.071	-0.73115
45	2.5	3	32.6	0	34.397	38.384	-0.73317
45	3	2	1.99	0	1.9159	12.213	-0.06414
45	3	3	34	0	33.845	42.166	-0.13885
45	3.5	2	1.27	0	0.96077	7.4308	0.52245
45	3.5	3	31.8	0	31.798	42.577	-0.16143
45	4	2	0.902	0	0.48181	4.5212	0.82362
45	4	3	30	0	29.179	41.005	0.15684
45	4	5	865.87	0	849.52	821.1	0.22877
45	4	4	873.17	0	900.33	1369.1	-1.087
45	4.5	2	0.514	0	0.24162	2.7509	0.54456
45	4.5	3	28.4	0	26.453	38.405	0.65735
45	5	2	0.456	0	0.12117	1.6737	0.69283

45	5	3	25.6	0	23.838	35.366	0.70281
45	6	3	20.2	0	19.244	29.196	0.54608
45	8	4	899.9	0	906.27	1421.3	-0.8679
45	8	5	1651.4	0	1588.3	1822.8	0.090918
45	8.05	2	0.508	0	0.001799	0.080801	1.0734
45	8.05	3	11.8	0	12.518	19.056	-0.35156
45	10	2	0.404	0	0.000122	0.011638	0.85665
45	10	3	8.28	0	8.5753	12.852	-0.02839
45	12	3	5.74	0	6.0599	8.8911	-0.12463
45	12	4	925.77	0	906.3	1422.3	-0.46439
45	12	5	1954.6	0	1917.5	2271.5	-0.11229
45	24	3	2.72	0	1.8063	2.4226	2.1205
45	24	4	944.57	0	906.3	1422.3	-0.17042
45	24	5	2238.8	0	2270.9	2722.1	-0.35376
45	36	5	2288.1	0	2424.1	2907	-0.65116
45	36.05	3	1.092	0	1.0458	1.3823	0.20509
45	48	3	0.814	0	0.65813	0.86607	0.42698
45	48	5	2303.4	0	2517.6	3019.1	-0.85745
46	0	1	0	7640	0	0	0
46	0.333	2	6.02	0	4.8178	5.7281	2.7739
46	0.5	3	0.428	0	0.073911	0.065823	0.80845
46	0.5	2	15.38	0	15.046	28.823	1.9538
46	0.75	3	1.146	0	0.77096	0.93495	0.75255
46	0.75	2	22.2	0	28.212	66.597	-0.46889
46	1	3	2.66	0	2.9803	3.9908	-0.97472
46	1	2	23	0	35.643	74.517	-2.0531
46	1.25	3	5.8	0	7.2128	9.5163	-2.4302
46	1.25	2	25.8	0	38.849	65.071	-2.2087
46	1.5	3	12.14	0	13.403	16.466	-1.9265
46	1.5	2	29	0	39.246	52.482	-1.8159
46	2	3	31.8	0	29.589	29.758	-0.39121
46	2	2	32	0	35.382	32.33	-0.73392
46	2	5	145.33	0	119.5	145.75	0.31515
46	2	4	554.21	0	628.94	1034	-2.6998
46	2.5	2	33.8	0	29.061	19.69	1.1174
46	2.5	3	48.6	0	46.577	38.384	-0.42944
46	3	2	34.4	0	22.612	11.981	3.694
46	3	3	63.2	0	60.486	42.166	0.020014
46	3.5	2	22.4	0	16.984	7.29	2.0937
46	3.5	3	73.8	0	69.585	42.577	0.61141
46	4	2	11.56	0	12.443	4.4356	-0.83324
46	4	3	82	0	73.789	41.005	1.4809
46	4	5	1100.1	0	1040.5	821.1	-0.46098

46	4	4	1237.3	0	1171.3	1369.1	-0.59094
46	4.5	2	8.08	0	8.9494	2.6988	-1.0499
46	4.5	3	72.6	0	73.896	38.405	0.39873
46	5	2	4.14	0	6.3461	1.642	-2.6645
46	5	3	72.8	0	70.999	35.366	0.96652
46	6	2	1.22	0	3.0917	0.60788	-3.3217
46	6	3	63.2	0	60.248	29.196	1.1755
46	8	3	38.6	0	36.219	19.256	0.67157
46	8	4	1395.3	0	1368.9	1421.3	0.040146
46	8	5	2873.7	0	2926.1	1822.8	0.58171
46	10	3	18.62	0	20.009	12.852	-1.2851
46	12	4	1407.9	0	1378.5	1422.3	0.22742
46	12	5	3580.3	0	3608	2271.5	1.1444
46	12.117	3	10.4	0	10.874	8.7133	-1.1341
46	24	3	2.34	0	2.0775	2.4226	0.38924
46	24	4	1407.9	0	1378.9	1422.3	0.23454
46	24	5	3775.9	0	4025.5	2722.1	0.62019
46	36	3	1.196	0	1.1712	1.3851	-0.03204
46	36	5	3797	0	4176.2	2907	0.30417
46	48.1	3	0.932	0	0.68196	0.86273	0.51694

List of Publications

Faisal M, Cawello W, Burckhardt BB, de Hoon J and Laer S (2019) Simultaneous Semi-Mechanistic Population Pharmacokinetic Modeling Analysis of Enalapril and Enalaprilat Serum and Urine Concentrations From Child Appropriate Orodispersible Minitablets. **Frontiers in. Pediatrics.** 7:281 (Accepted).

Faisal M, Cawello W, Burckhardt BB, Läer S. Model-dependent pharmacokinetic analysis of enalapril administered to healthy adult volunteers using orodispersible minitablets for use in pediatrics**. Drug design development therapy** (2019) 13 (Dove press 6354687), pp. 481-490.

Mahmood Ahmad*, Muhammad Usman Minhas, Muhammad Sohail, Muhammad Faisal, Haroon Rashid. Comprehensive Review of Magnetic Drug Delivery Systems: A Novel Approach for Drug Targeting. **Journal of Pharmacy and Alternative Medicine**, 2013, 2(4): 13-21.

Faisal M, Cawello W, Läer S. Simultaneous population pharmacokinetic analysis of enalapril in serum and urine administered using orodispersible mini-tablets for use in children. **ASCPT** Washington, USA, Poster Session (PIII-042), **Clinical Pharmacology and Therapeutics** (2019) 105 (S1), p S94 https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1344.

Faisal M, Cawello W, Läer S. Pharmacokinetic comparison of enalapril administered using market authorized and child-appropriate dosage formulations. **ACCP** Seattle, USA, Poster Sessions; **JACCP** (2018) 1(2), p. 265, Poster (382) https://accpjournals.onlinelibrary.wiley.com/doi/full/10.1002/jac5.1059.

Faisal M, Cawello W, Läer S. Simultaneous semi-mechanistic population pharmacokinetic analysis of enalapril and enalaprilat in serum and urine following the administration of child-appropriate oro-dispersible mini-tablets. **PAGE** 28 (2019) Abstr 8955 [www.page-meeting.org/?abstract=8955]

Reports, Manuals, Analysis Plan.

Manual and population pharmacokinetic analysis plan; Manual for LENA pharmacokinetic and pharmacodynamic analysis of pediatric patients of heart failure and dilated cardiomyopathy (WP08/09/10).

A Pharmacokinetic report has been written on the topic; Comparative analysis of 3 different treatments of enalapril by compartmental pharmacokinetic model analysis.

A Pharmacokinetic report has been written on the topic; Enalaprilat compartmental pharmacokinetic modeling analysis using Phoenix WinNonlin.

A Pharmacokinetic report has been written on the topic; Non-compartmental analysis with serum concentrations of enalapril and enalaprilat measured in samples of study WP09 (Congenital Heart Disease).

A Pharmacokinetic report has been written on the topic; Non-compartmental analysis with serum concentrations of enalapril and enalaprilat measured in samples of study WP08 (Dilated cardiomyopathy Disease).

Module II has been written for EU submission on the topic; A systematic review of the safety, efficacy, pharmacokinetics, and pharmacodynamics of enalapril in pediatrics suffering from congestive heart failure and dilated cardiomyopathy.

Presentations

Scientific poster presentation at the Global conference of the American College of Clinical Pharmacy (**ACCP**), held at Seattle, The USA 20-23 October 2018. Topic; Pharmacokinetic comparison of enalapril administered using market authorized and child-appropriate dosage formulations.

Scientific poster presentation at the American Society of Clinical Pharmacology and Therapeutics (**ASCPT**), held at Washington DC, The USA March 2019. Topic; Simultaneous population pharmacokinetic analysis of enalapril in serum and urine administered using orodispersible mini-tablets for use in children.

Presented poster entitled “Physiological Based Pharmacokinetic Modelling”: A Translational Approach in Pediatric Pharmacokinetics” at 3rd Annual International Pharmacy Scientific Symposium & Pharmaceutical Exhibition on “Bridging Pharmacy Practice & Research”, March 28-30, 2014, at Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan.

Presented poster entitled “Pharmacokinetic comparison of enalapril administered using market authorized and child-appropriate dosage formulations” at Pharmacometrics NRW meeting, Cologne (July 2018).

Conferences and Training

Attended the Uppsala Summer School focused on covariate model building and PKPD modeling of continuous and categorical data held in Uppsala Sweden from 12th August to 24th August 2019.

Attended the Twenty seventh-population approach group in Europe (PAGE) meeting held in Montreux, Switzerland 27.05.2018 to 1.06.2018.

The five-day workshop titled "Hands-on Experience with Model-based drug development: Incorporating population variability into mechanistic prediction of PK and modeling PK/PD" by Certara at Basel (Switzerland). March 2017.

Attended the Pharmacometrics NRW meeting, Cologne, Germany (July 2018).

Series of course delivered by Dr. Willi Cawello (UCB pharmaceuticals, Germany) on "Population pharmacokinetic modeling" (Start: SS 18.04.2017 --- End: WS 30.03. 2018).

One day training on "Good Clinical Laboratory Practices" held at Heinrich Heine University on 19/10/2016.

Two days iGRAD workshop "Success in Companies: How to establish yourself and your projects in a business environment" on 27/28 October 2016.

One-day seminar attended on "Good Scientific Practice for Doctoral Researchers". August 17/2016.

Two days iGRAD workshop on "Leadership skills for scientists" held on 14/15 October 2019.

Attended 15th International Pharmacy Conference & Exhibition on "Pharmacy Profession for Prosperous Health", held on 5th-8thth April 2009, at PC, Lahore.

Two days iGRAD workshop "Get into Teaching: on 7/8/ October 2019.

Attended a seminar on topic "Patient safety and pharmacovigilance", held on 7th-June 2014, at Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan.

Software Expertise

Expert Level: I have used NONMEM, Phoenix WinNonlin/NLME, Pirana, R, PsN, Microsoft Excel/Word/PowerPoint for over 3.5 years. I have used PK-SIM and SimCYP for 2 years

Awards

Fully funded DAAD scholarship awarded for 4 years to do Ph.D in Germany

ASCPT travel grants were awarded by ASCPT sponsored by Genentech pharmaceuticals (Roche) to present research work at the Annual conference of the American Society of Clinical Pharmacology and Therapeutics ASCPT 2019.

HERA travel grants were awarded in 2018 for the presentation of research work at the Global conference of the American College of Clinical Pharmacy (ACCP).

Memberships

- Member of the International Society of Pharmacometrics (ISOP) organization
- Member of the American Society of Clinical Pharmacology and Therapeutics (ASCPT) organization
- Member of the American College of Clinical Pharmacy (ACCP)
- Member of Interdisciplinary Graduate and Research Academy Dusseldorf, Germany (IGRAD)

Reference

1. Ph. D supervisor: Professor Stephanie Läer

Title: Head of the Institute of Clinical Pharmacy and Pharmacotherapy, Heinrich Heine Dusseldorf, Germany. Email: stephanie.laeer@uni-duesseldorf.de.

2. Dr Willi Cawello

Title: Former Principal Quantitative Scientist. Global Biostatistics UCB Bio-Sciences GmbH. Monheim, Germany. Email: cawello@uni-duesseldorf.de.