

DETERMINING THE PHARMACOKINETICS AND PHARMACODYNAMICS OF  
ANTIBIOTICS IN PREMATURE INFANTS

Michael Cohen-Wolkowicz, M.D.

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences in the Eshelman School of Pharmacy (Division of Pharmacotherapy and Experimental Therapeutics).

Chapel Hill  
2012

Approved by:

Angela D. M. Kashuba, PharmD

Daniel K. Benjamin Jr., MD, MPH, PhD

Dhiren Thakker, PhD

Daniele Ouellet, PhD

Ralph Raasch, PharmD

©2012  
Michael Cohen-Wolkowicz, M.D.  
ALL RIGHTS RESERVED

## ABSTRACT

MICHAEL COHEN-WOLKOWIEZ: Determining the Pharmacokinetics and Pharmacodynamics of Antibiotics in Premature Infants  
(Under the direction of Angela D. M. Kashuba, Daniel K. Benjamin Jr., Dhiren Thakker, Daniele Ouellet, and Ralph Raasch)

In the United States, approximately 13% of the annual birth cohort is born preterm (<37 weeks gestational age). These infants are at high risk of systemic infections, and most are treated with antimicrobial agents. In spite of their common use, antimicrobials lack pharmacokinetic (PK) data in preterm infants. Extrapolation of dosing information from older children and adults to preterm infants often results in therapeutic failures or unwanted toxicities. Therefore, PK studies in this population are needed. Unique challenges posed by preterm infants, however, limit the ability to evaluate drug disposition in this population. Novel, minimal-risk methods can provide the platform to overcome these challenges and optimize antimicrobial dosing. In this proposal, several of these methods were employed to deliver antimicrobial dosing recommendations specifically designed for preterm infants. Two commonly used antimicrobials, piperacillin and metronidazole, were used to evaluate the utility of these methods. A multiplex liquid chromatography-tandem mass spectrometry assay for the simultaneous quantification of ampicillin, piperacillin, tazobactam, meropenem, acyclovir, and metronidazole in ultra-low (<50 uL) human plasma was developed and validated. This method was used to analyze drug concentration data from sparse, scavenged, and dried blood spot PK samples collected from preterm infants <32 weeks gestational age at birth. The scavenged concentration data were analyzed by population PK methodologies and

used to derive PK parameters and identify covariates (serum creatinine and postmenstrual age) that explain inter-individual variability in piperacillin and metronidazole clearance. When compared to historical data from small studies using traditional PK sampling, piperacillin concentrations were 2–10-fold lower in the scavenged sampling approach, which prevented the determination of optimal dosing recommendations for piperacillin. In contrast, scavenged sampling proved successful for metronidazole and allowed for the development of a simplified, postmenstrual age-based dosing regimen. Piperacillin and tazobactam dried blood spot sampling proved successful as a proof-of-concept application. Dried blood spot piperacillin and tazobactam concentrations can be used as surrogate for plasma measurements. Novel, minimal-risk methods are powerful tools to evaluate the pharmacokinetics/pharmacodynamics of antimicrobials in preterm infants. The success of these methods is drug-dependent, and they should be systematically studied prior to universal implementation.

## ACKNOWLEDGMENTS

I wish to acknowledge and thank all of my committee members (Drs. Angela Kashuba, Danny Benjamin, Daniele Ouellet, Dhiren Thakker, and Ralph Raasch) for providing me with guidance and support during my Ph.D. degree. I especially want to thank Dr. Angela Kashuba for welcoming me into her lab with an open mind and Dr. Daniele Ouellet for her availability to provide technical guidance.

I want to offer my sincerest gratitude to mentor and committee member, Dr. Danny Benjamin, who has offered full-fledged support of my career development and overall career path over the five years at Duke University.

I wish to thank the NICHD at the National Institutes of Health for my K23 Career Development Award.

I would like to thank my family, who define unconditional support.

## TABLE OF CONTENTS

LIST OF TABLES .....	viii
LIST OF FIGURES .....	x
LIST OF ABBREVIATIONS.....	xii
INTRODUCTION .....	1
Chapter	
I.    DEVELOPMENT OF A LIQUID CHROMATOGRAPHY- TANDEM MASS SPECTROMETRY ASSAY OF SIX ANTIMICROBIALS IN PLASMA FOR PHARMACOKINETIC STUDIES IN PREMATURE INFANTS.....	9
Introduction.....	9
Methods.....	10
Results.....	17
Discussion.....	19
II.   POPULATION PHARMACOKINETICS OF PIPERACILLIN USING SCAVENGED SAMPLES FROM PRETERM INFANTS .....	38
Introduction.....	38
Methods.....	39
Results.....	44
Discussion.....	48
III.  POPULATION PHARMACOKINETICS OF METRONIDAZOLE USING SCAVENGED SAMPLES FROM PRETERM INFANTS .....	64

Introduction.....	64
Methods.....	66
Results.....	71
Discussion.....	74
<b>IV. PIPERACILLIN AND TAZOBACTAM IN DRIED BLOOD SPOTS: ASSAY DEVELOPMENT AND CLINICAL APPLICATION IN PRETERM INFANTS.....</b>	<b>97</b>
Introduction.....	97
Methods.....	98
Results.....	104
Discussion.....	106
<b>SUMMARY AND FUTURE DIRECTIONS.....</b>	<b>124</b>
<b>APPENDICES.....</b>	<b>130</b>
Appendix 1: Metronidazole Final Model Control File and Output .....	130
Appendix 2: Metronidazole PK Dataset .....	137
Appendix 3: Piperacillin Final Model Control File and Output .....	155
Appendix 4: Piperacillin PK Dataset .....	163
<b>REFERENCES FOR SUMMARY.....</b>	<b>198</b>

## LIST OF TABLES

### Table

1.1.	Individual stock solutions .....	24
1.2.	Optimal precursor and product ions and instrument parameters by compound.....	25
1.3.	Summary of standard curve, retention times, and extraction efficiency.....	26
1.4.	Matrix effects .....	27
1.5.	Summary of accuracy and precision .....	29
1.6.	Drug concentrations in patient samples .....	30
2.1	Clinical data by gestational age group .....	54
2.2	Model-building process .....	55
2.3	Final population pharmacokinetic model parameter estimates.....	56
2.4	Individual empirical Bayesian pharmacokinetic parameter estimates by gestational age group .....	57
3.1.	Dosing schemes used to assess pharmacodynamic target achievement .....	82
3.2.	Clinical data by gestational age group .....	83
3.3.	Model-building process .....	84
3.4.	Final population pharmacokinetic model parameter estimates.....	85
3.5.	Individual empirical Bayesian pharmacokinetic parameter estimates by gestational age group .....	86
4.1.	Optimal precursor and product ions and instrument parameters by compound.....	111



4.2.	Summary of standard curve, retention times, and extraction efficiency.....	112
4.3.	Summary of accuracy and precision.....	113
4.4.	Validation of piperacillin partial dilutions.....	114
4.5.	DBS and plasma concentrations for piperacillin and tazobactam .....	115

## LIST OF FIGURES

### Figure

1.1.	Blank plasma sample run in a) negative (tazobactam) and b) positive (top to bottom: metronidazole, acyclovir, ampicillin, meropenem, piperacillin) ionization mode .....	32
1.2.	Lower limit of quantification in a) negative (top to bottom: tazobactam and dicloxacillin [IS]) and b) positive (top to bottom: dicloxacillin [IS], metronidazole, acyclovir, ampicillin, meropenem, piperacillin) ionization mode. Upper limit of quantification in c) negative (top to bottom: tazobactam and dicloxacillin [IS]) and d) positive (top to bottom: dicloxacillin [IS], metronidazole, acyclovir, ampicillin, meropenem, piperacillin) ionization mode.....	34
2.1.	Base model scatter plots of CL ETA1 estimates and the following: BGA (A), PNA (B), PMA (C), and SCR (D) .....	58
2.2.	Final population pharmacokinetic model diagnostic plots: observed vs. population prediction (A) and individual prediction (B), weighted residuals vs. population predictions (C) and time (D).....	59
2.3.	Visual predictive check of piperacillin dose-normalized concentrations versus time .....	60
2.4.	Weight-normalized piperacillin clearance versus serum creatinine (A) and body weight (B).....	61
2.5.	Pharmacodynamic target attainment rates by gestational age group .....	62
3.1.	Base model scatter plots of CL ETA1 estimates and the following: BGA (A), PNA (B), PMA (C), and SCR (D).....	87
3.2.	Final population PK model diagnostic plots: observed vs. population predictions (A) and individual predictions (B); weighted residuals vs. population predictions (C) and time (D) .....	88
3.3.	Visual predictive check of metronidazole concentrations versus time .....	89
3.4.	Weight-normalized metronidazole clearance versus postmenstrual age (A) and serum creatinine (B).....	90

3.5.	PD target attainment rates by gestational age group: proportion of study subjects who met PD target with dosing prescribed per routine medical care (A); predicted steady-state metronidazole trough concentrations in study subjects (B); proportion of simulated subjects who met PD target with different dosing schemes (C); and predicted steady-state metronidazole trough concentrations in simulated subjects (D) .....	91
3.6.	PD target attainment rates by gestational age group and postnatal age in simulated subjects: GA group <26 weeks (A); GA group 26–29 weeks (B); GA group 30–32 weeks (C).....	93
3.7.	Simulated time-concentration profiles with proposed PMA dosing regimen in typical subjects: PMA 26 weeks, weight 900 g (A); PMA 32 weeks, weight 1900 g (B); PMA 36 weeks, weight 2800 g (C); PMA 41 weeks, weight 3800 g (D) .....	95
4.1.	Blank plasma sample run in a) negative (tazobactam top, IS bottom) and b) positive (piperacillin top, IS bottom) ionization mode .....	116
4.2.	Lower limit of quantification in a) negative (top to bottom: Tazobactam and dicloxacillin [IS]) and b) positive (top to bottom: dicloxacillin [IS], piperacillin) ionization mode. Upper limit of quantification in c) negative (top to bottom: tazobactam and dicloxacillin [IS]) and d) positive (top to bottom: dicloxacillin [IS], piperacillin) ionization mode .....	118
4.3.	On card stability for piperacillin (gray line) and tazobactam (black line) .....	122
4.4.	Scatter plots of DBS vs. plasma concentrations for a) piperacillin and b) tazobactam .....	123

## LIST OF ABBREVIATIONS

BGA	birth gestational age
BLD	below the level of detection
BLQ	below the level of quantification
BPCA	Best Pharmaceuticals for Children Act
CI	confidence interval
CL	clearance
CLSI	Clinical and Laboratory Standards Institute
CV	coefficient of variation
DBS	dried blood spots
DMSO	dimethyl sulfoxide
FDA	Food and Drug Administration
EDTA	ethylenediaminetetraacetic acid
Hct	hematocrit
HPLC	high-performance liquid chromatography
IIV	inter-individual
IS	internal standard
LLOQ	lower limit of quantification
MIC	minimum inhibitory concentration
MS	mass spectrometry
NIH	National Institutes of Health
NONMEM	nonlinear mixed effect modeling

OFV	objective function value
PD	pharmacodynamics
PK	pharmacokinetics
PMA	postmenstrual age
PNA	postnatal age
POPS	Pediatric Opportunistic PK Study
PPRU	Pediatric Pharmacology Research Unit
QC	quality control
RSE	relative standard error
RV	residual variability
SCR	serum creatinine
SD	standard deviation
ULOQ	upper limit of quantification
V	volume

## INTRODUCTION

Infections in preterm infants are common and fatal.<sup>1,2</sup> Approximately 20% of very-low-birth-weight (<1500 g) infants suffer from culture-proven sepsis, and 10–20% die from sepsis in spite of antimicrobial therapy.<sup>1,2</sup> Among extremely-low-birth-weight (<1000 g) infants, infection is associated with poor neurodevelopmental outcomes.<sup>3</sup> To prevent these devastating consequences, more than 90% of infants born <33 weeks gestational age who are admitted to the nursery are treated with multiple antimicrobial agents.<sup>4</sup>

In spite of their common use, over 50% of antimicrobials are prescribed off-label in the nursery,<sup>5–7</sup> and most lack some aspect of pharmacokinetic (PK) information specific to infants. Off-label prescribing based on extrapolation of dosing recommendations from older children or adults results in adverse drug effects or lack of efficacy.<sup>8–10</sup> The latter is likely due to the unique and complicated physiology of preterm infants, which differs greatly from older children and adults. These differences include a larger extracellular fluid volume, immature renal and hepatic function, underdevelopment of metabolic enzymatic systems, and a unique blood-brain barrier—all of which can alter drug disposition significantly.<sup>11</sup> As a result, antibiotic dosing used in adults (normalized by body weight) and extrapolated to premature infants may result in efficacy failures or unwanted toxicity. The combination of these factors underscores the critical need for PK and safety studies specifically designed for the preterm infant population.

Several limitations inherent to trials involving preterm infants, however, prevent researchers from pursuing the study of drugs in this population. These include low rates of informed consent among parents of critically ill infants; limited blood volume necessary to conduct PK studies; lack of availability of sensitive multiplexed analytical methods to measure drug concentrations; lack of population PK analysis expertise in the pediatric field capable of analyzing sparse PK data; and difficulties associated with pre-specified timing of blood samples for PK analysis.

To overcome these challenges, novel minimal-risk methods to evaluate the PK of antimicrobials in infants are needed. These methods include sparse and scavenged sampling, multiplex drug assays in ultra-low plasma volumes, population PK analyses using pediatric data, and alternative biological matrices such as dried blood spots (DBS). Even though the implementation of these methods could result in specific dosing recommendations for preterm infants, most have not been systematically studied in this population.

A minimal-risk method to obtain sparse samples is the collection of scavenged samples left over from the normal clinical care of infants. Once collected, these samples are sent to clinical laboratories for chemical and hematological assays. Blood sent to laboratories is often in excess of what is needed for the laboratory assay, and this surplus can be saved for PK analysis. The use of scavenged samples for PK studies in preterm infants offers several advantages over traditional timed PK trials. These include avoiding the need for heel sticks specifically for the study; higher rates of parental consent; availability of several samples per infant; and avoidance of time-specific sampling. Possible disadvantages include drug stability problems associated with inappropriate sample storage; unsuitable draw times not useful for PK analysis; and low volume of surplus blood. Most of these limitations can be

overcome by the availability of several samples per patient, use of new methodologies for estimating PK parameters such as population PK analyses, and sensitive multi-drug concentration assays that can detect several drugs in the same sample.

The use of sparse sampling and population PK approaches have been most extensively studied with drugs such as vancomycin and gentamicin because these agents are subjected to routine therapeutic drug monitoring in the clinical setting. Other drugs for which this type of analysis has proven successful in preterm infants include fluconazole,<sup>12</sup> cefepime,<sup>13</sup> and amoxicillin.<sup>14</sup> In these studies, the use of sparse sampling resulted in changes of dosing recommendations for preterm infants.

Another methodology that could advance PK studies in preterm infants is multiplexed bioanalytical chemistry methods that can simultaneously measure multiple drugs in ultra-low (<100  $\mu$ L) plasma volumes.<sup>15</sup> Using the simultaneous measuring approach, this technology maximizes the drug concentration information obtained from each PK sample. This methodology has been successful in several settings including measurement of 17 antiretroviral drugs from different drug classes in 50 $\mu$ L of human plasma<sup>16</sup> and simultaneous measurements of 5 beta-lactam antibiotics (cefepime, ceftazidime, cefuroxime, meropenem, and piperacillin) and 7 antimicrobials (cefuroxime, cephalexin, ceftazidime, ampicillin, benzylpenicillin, metronidazole, and chloramphenicol) of different classes.<sup>17,18</sup> In infants, the multiplex-assay approach is attractive because they are often treated with several antimicrobials concomitantly. More importantly, in the setting of clinical trials where each infant receives a different antimicrobial agent, a single multiplex assay increases trial efficiency by measuring drug concentrations of all agents without the need to develop and validate multiple individual assays specific for each drug.



Even though novel, ultra-sensitive bioanalytical assays have substantially decreased the amount of plasma required to measure drug concentrations in preterm infants, traditional PK plasma sampling still involves the collection of ~200  $\mu$ L of whole blood for each PK sample. This requirement is due to the need for separation of plasma or serum from the cellular components of whole blood. As such, the blood volume required per sample is usually double the amount of plasma needed for analysis, thereby increasing the amount of sample collected unnecessarily. In addition, sample processing times and personnel training are required to maintain a controlled sample collection environment. Over the past few years, a novel sample collection method using DBS has emerged and is increasingly employed by the pharmaceutical industry in drug development.<sup>19</sup> This method involves the collection of 15–30  $\mu$ L of whole blood on blotting paper. Potential advantages of this approach include low sample volume, minimal personnel training, no sample processing (sample is collected as a final product at the patient bedside), room temperature storage, and simple sample extraction. These properties make DBS sampling an attractive technology for PK sampling in infants.

DBS sampling has been used in the newborn metabolic diseases screening program over the past 5 decades; however, its application in clinical PK trials is limited. Several investigators have successfully demonstrated the ability of DBS to reflect traditional whole blood and plasma drug concentrations in adult clinical trials.<sup>20–22</sup>

The studies conducted under this dissertation proposal involve the use of minimal-risk methods to evaluate the PK/pharmacodynamics (PD) of antimicrobials in preterm infants. Two antimicrobials, piperacillin and metronidazole, were chosen to evaluate the utility of these minimal-risk methods. These antimicrobials were selected because they are

commonly used in preterm infants, there is minimal PK/PD information in the published literature, they exhibit different elimination pathways, and they possess different physicochemical properties, all of which can alter the success of the minimal-risk methods evaluated. The combination of these factors will allow the thorough evaluation of these methods to determine the most useful tools to evaluate the PK/PD of antimicrobials in preterm infants and revolutionize the way PK studies are conducted in this vulnerable population.

The hypothesis of this proposal is that scavenged blood samples can be used in infants to generate antimicrobial PK/PD relationships and provide evidence-based dosing recommendations. Additionally, dried blood spot technology can provide similar data to plasma sampling with less invasive collection techniques.

AIM 1: Develop and validate a multiplex drug concentration assay containing ampicillin, piperacillin/tazobactam, acyclovir, metronidazole, and meropenem in 50 uL of infant plasma using mass spectrometry with a lower limit of quantification appropriate for scavenged sampling. A high-performance liquid chromatography-tandem mass spectrometry method will be developed and validated according to Food and Drug Administration criteria to measure drug concentrations of 5 commonly used antimicrobials in 50 uL of infant plasma with intra- and interday accuracy and precision of 85–125% and >80%, respectively.

AIM 2: Determine the pharmacokinetics and pharmacodynamics of piperacillin and metronidazole in premature infants using scavenged samples.

AIM 2a: Develop a pharmacokinetic model of piperacillin and metronidazole in premature infants. Developing this model will show that the clearance of

piperacillin and metronidazole are directly related to postmenstrual age, requiring new dosing recommendations adjusted by this factor.

AIM 2b: Determine the likelihood of achieving an optimal pharmacodynamic target for piperacillin and metronidazole with current dosing recommendations. This analysis will demonstrate that current dosing recommendations for piperacillin and metronidazole will achieve the optimal pharmacodynamic target in less than 50% of infants. The target for piperacillin use in bacteremia is a time above the minimum inhibitory concentration-90 of at least 75% of the dosing interval; the target for metronidazole use in intra-abdominal infections is trough concentrations higher than 8 mg/L.

AIM 3: Determine the comparability of piperacillin drug concentrations in plasma and dried blood spots samples. For piperacillin, an optimal blood spot extraction method will be developed and stability will be quantified. The comparability between piperacillin drug concentrations in plasma and dried blood samples will be evaluated.

## References

1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2 Pt 1):285–291.
2. Stoll BJ, Hansen NI, Higgins RD, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002–2003. *Pediatr Infect Dis J*. 2005;24(7):635–639.
3. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA*. 2004;292(19):2357–2365.
4. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics*. 2006;117(6):1979–1987.
5. Avenel S, Bomkratz A, Dassieu G, Janaud JC, Danan C. [The incidence of prescriptions without marketing product license in a neonatal intensive care unit]. *Arch Pediatr*. 2000;7(2):143–147.
6. O'Donnell CP, Stone RJ, Morley CJ. Unlicensed and off-label drug use in an Australian neonatal intensive care unit. *Pediatrics*. 2002;110(5):e52.
7. 't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. A survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. *Pediatrics*. 2001;108(5):1089–1093.
8. Ferranti J, Horvath MM, Cozart H, Whitehurst J, Eckstrand J. Reevaluating the safety profile of pediatrics: a comparison of computerized adverse drug event surveillance and voluntary reporting in the pediatric environment. *Pediatrics*. 2008;121(5):e1201–e1207.
9. Choonara I. Unlicensed and off-label drug use in children: implications for safety. *Expert Opin Drug Saf*. 2004;3(2):81–83.
10. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA*. 2003;290(7):905–911.
11. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–1167.
12. Wade KC, Wu D, Kaufman DA, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother*. 2008;52(11):4043–4049.

13. Capparelli E, Hochwald C, Rasmussen M, Parham A, Bradley J, Moya F. Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother.* 2005;49(7):2760–2766.
14. Pullen J, Stolk LM, Nieman FH, Degraeuwe PL, van Tiel FH, Zimmermann LJ. Population pharmacokinetics and dosing of amoxicillin in (pre)term neonates. *Ther Drug Monit.* 2006;28(2):226–231.
15. Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA. Microanalysis of beta-lactam antibiotics and vancomycin in plasma for pharmacokinetic studies in neonates. *Antimicrob Agents Chemother.* 2009;53(1):75–80.
16. Jung BH, Rezk NL, Bridges AS, Corbett AH, Kashuba AD. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. *Biomed Chromatogr.* 2007;21(10):1095–1104.
17. Denooz R, Charlier C. Simultaneous determination of 5 beta-lactam antibiotics (cefepim, ceftazidim, cefuroxim, meropenem and piperacillin) in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2008;864(1-2):161–167.
18. Holt DE, de Louvois J, Hurley R, Harvey D. A high performance liquid chromatography system for the simultaneous assay of some antibiotics commonly found in combination in clinical samples. *J Antimicrob Chemother.* 1990;26(1):107–115.
19. Spooner N, Lad R, Barfield M. blood spots as a sample collection technique for the determination of pharmacokinetics in clinical studies: considerations for the validation of a quantitative bioanalytical method. *Anal Chem.* 2009;81(4):1557–1563.
20. Cheung CY, van der Heijden J, Hoogtanders K, et al. Dried blood spot measurement: application in tacrolimus monitoring using limited sampling strategy and abbreviated AUC estimation. *Transpl Int.* 2008;21(2):140–145.
21. Allanson AL, Cotton MM, Tettey JN, Boyter AC. Determination of rifampicin in human plasma and blood spots by high performance liquid chromatography with UV detection: a potential method for therapeutic drug monitoring. *J Pharm Biomed Anal.* 2007;44(4):963–969.
22. Hibberd SG, Alveyn C, Coombes EJ, Holgate ST. Acute and chronic pharmacokinetics of asymmetrical doses of slow release choline theophyllinate in asthma. *Br J Clin Pharmacol.* 1986;22(3):337–341.

## CHAPTER I: DEVELOPMENT OF A LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY ASSAY OF SIX ANTIMICROBIALS IN PLASMA FOR PHARMACOKINETIC STUDIES IN PREMATURE INFANTS

### Introduction

Infections in premature infants (<37 weeks gestation at birth) are common and fatal<sup>1,2</sup>; approximately 20% of very-low-birth-weight (<1500 g) infants suffer from culture-proven sepsis, and 10–20% die.<sup>1,2</sup> To prevent these devastating consequences, more than 90% of infants born <33 weeks gestational age and admitted to the nursery are treated with multiple antimicrobial agents.<sup>3</sup> In spite of the widespread use of antimicrobials in this population, pharmacokinetic (PK) studies in premature infants are exceptionally scarce. This is due, in part, to limitations inherent to trials involving premature infants, including limited blood volume necessary to conduct PK studies and lack of availability of sensitive and specific drug concentration assays.

Over the last 2 decades, advances in technology have provided tools to measure drug concentration in biological matrices accurately, selectively, and with increased sensitivity. Optimized methods using high-performance liquid chromatography (HPLC) and the incorporation of mass spectrometry (MS) have resulted in the ability to measure drug concentrations in low (<100 uL) plasma volume. In addition, given the ability of these instruments to separate compounds efficiently, it is now possible to measure several compounds in the same sample simultaneously.<sup>4</sup> This methodology has been successful in

several settings, including measurement of antiretroviral drugs from different drug classes<sup>5</sup> and simultaneous measurements of antimicrobials.<sup>6,7</sup> In premature infants, the multiplex-assay approach is attractive because these patients are often treated with several antimicrobials concomitantly. More importantly, in the setting of clinical trials where each infant receives a different antimicrobial agent, a single multiplex assay increases trial efficiency by measuring drug concentrations of all agents without the need to develop and validate multiple individual assays specific for each drug. Therefore, the purpose of this work was to develop and validate a LC–MS/MS multiplex drug concentration assay for commonly used antimicrobials in premature infants, including ampicillin, piperacillin, tazobactam, meropenem, acyclovir, and metronidazole.

## Methods

### *Chemicals and reagents*

Ampicillin, piperacillin, acyclovir, metronidazole, and dicloxacillin (internal standard [IS]) were purchased from the Sigma Chemical Company (St. Louis, MO, USA). Tazobactam and meropenem were purchased from the U.S. Pharmacopeia (Rockville, MD, USA). HPLC-grade chemicals were purchased from Fisher Scientific (Norcross, GA, USA). Purified compressed nitrogen was obtained from Airgas-National Welders (Charlotte, NC, USA). Drug-free pooled plasma was obtained from Biological Specialty Corporation (Colmar, PA, USA). Plasma obtained from whole blood anticoagulated with potassium triphosphate ethylenediaminetetraacetic acid (EDTA) was obtained from Biological Specialty Corporation.

### *Equipment*

Compounds were analyzed with a triple quadrupole mass spectrometer API 4000 (Applied Biosystems–ABSciex, Foster City, CA, USA). A Shimadzu solvent delivery system (Columbia, MD, USA), LEAP HTC PAL thermostatted autosampler (Carrboro, NC, USA), Valco switching valve (Houston, TX, USA), and Analyst Software version 1.4.1 (Applied Biosystems–ABSciex, Foster City, CA, USA) run on a Dell desktop computer (operated by Windows XP professional) were used for this method.

### *Preparation of standards*

Individual clear stock solutions of ampicillin, piperacillin, tazobactam, meropenem, acyclovir, and metronidazole were prepared at the following concentrations: ampicillin, piperacillin, and tazobactam 15 mg/mL, meropenem and acyclovir 5 mg/mL, and metronidazole 2.5 mg/mL. Each analyte was accurately weighed and dissolved in dimethyl sulfoxide (DMSO) according to Table 1.1.

The master stock solution was prepared as a composite of all 6 compounds (0.5 mL each), adjusted to a final concentration of 1,500,000 ng/mL for ampicillin, piperacillin, and tazobactam; 500,000 ng/mL for meropenem and acyclovir; and 250,000 ng/mL for metronidazole, by 2.0 mL of DMSO. This master stock standard was used to prepare 7 intermediate composite stock solutions: ampicillin and piperacillin (1,500,000; 750,000; 300,000; 150,000; 30,000; 15,000; and 3,000 ng/mL); tazobactam (750,000; 300,000; 150,000; 30,000; 15,000; 3,000; and 1,500 ng/mL); meropenem and acyclovir (500,000; 250,000; 100,000; 50,000; 10,000; 5,000; and 1,000 ng/mL); and metronidazole (250,000; 125,000; 50,000; 25,000; 5,000; 2,500; and 500 ng/mL) in DMSO.



Plasma working calibration solutions at 150,000, 75,000, 30,000, 15,000, 3,000, 1,500, and 300 ng/mL for ampicillin and piperacillin; 75,000, 30,000, 15,000, 3,000, 1,500, 300, and 150 ng/mL for tazobactam; 50,000, 25,000, 10,000, 5,000, 1,000, 500, and 100 ng/mL for meropenem and acyclovir; and 25,000, 12,500, 5,000, 2,500, 500, 250, and 50 ng/mL for metronidazole were prepared by diluting the intermediate solutions in human drug-free plasma in a ratio of 1:9.

From the master and intermediate stock solutions, quality control (QC) intermediate stock solutions were prepared in DMSO at concentrations of 9,000, 600,000, and 1,200,000 ng/mL for ampicillin and piperacillin; 4,500, 180,000, and 600,000 ng/mL for tazobactam; 3,000, 200,000, and 400,000 ng/mL for meropenem and acyclovir; and 1,500, 100,000, and 200,000 ng/mL for metronidazole. Plasma working QC samples of 900, 60,000, and 120,000 ng/mL for ampicillin and piperacillin; 450, 18,000, and 60,000 ng/mL for tazobactam; 300, 20,000, and 40,000 ng/mL for meropenem and acyclovir; and 150, 10,000, and 20,000 ng/mL for metronidazole were prepared by diluting the QC intermediate solutions in human drug-free plasma in a ratio of 1:9.

#### *Internal standard preparation*

Dicloxacillin (1 mg) was weighed and dissolved in DMSO to achieve a final concentration of 1.0 mg/mL (stock solution). The internal standard working solution was prepared by diluting 0.3 mL of this solution in 99.7 mL of acetonitrile to achieve a final concentration of 3,000 ng/mL.

### *Samples and pre-treatment*

This method was used to measure antimicrobial concentrations in clinical samples collected from premature infants at pre-specified time points or scavenged from the clinical laboratory after processing for clinical care. Sample collection (~200–1000  $\mu\text{L}$ , heparinized or EDTA tubes) occurred under an investigational protocol approved by the institutional review board at participating sites and after informed consent was obtained from caregivers of study participants. Blood samples at pre-specified time points were collected and kept on ice after collection for a maximum of 15 minutes. Blood plasma was separated by centrifugation for 10 minutes. Plasma samples were transferred to a  $-80^{\circ}\text{C}$  temperature-monitored freezer for storage until analysis. Prior to extraction, all plasma samples were brought to room temperature and then gently mixed.

### *The extraction procedure*

On the day of analysis, 200  $\mu\text{L}$  of chilled (left in the refrigerator for 20 minutes) internal standard was placed into a 2.0 mL labeled conical plastic Eppendorf tube, followed by 45  $\mu\text{L}$  of plasma and 5  $\mu\text{L}$  of DMSO (for blank and patient samples) or by 50  $\mu\text{L}$  of spiked plasma (for calibrators and QC samples). The DMSO was added to the blank and patient samples to compensate for the DMSO added to the plasma working calibration solutions. The solutions were vortex-mixed for 15 minutes and centrifuged at 15,600 g at  $4^{\circ}\text{C}$  for 10 minutes. The supernatant portion was transferred into a 96-insert holder with 0.7 mL glass inserts (Q Glass, NJ, USA). The inserts on the holder were tightly sealed with a silicone 96-insert cover.

### *LC-MS/MS analysis*

Ampicillin, piperacillin, acyclovir, meropenem, and metronidazole were analyzed in positive mode. Tazobactam was analyzed in negative mode during a separate injection run from the same glass insert. Dicloxicillin was used as internal standard for both positive and negative analyses. The injection volume was 4  $\mu$ L.

Chromatography was achieved by using a reverse-phase C18 Aquasil column (50 x 2.1-mm internal diameter, 5  $\mu$ m particle size; Thermo Fisher, Waltham, MA, USA) with a flow rate of 0.75 ml/min for analysis in positive mode and a C18 Ultra Aqueous column (50 x 2.1-mm internal diameter, 3  $\mu$ m particle size; Restek, Bellefonte, PA, USA) with a flow rate of 0.35 ml/min for analysis in negative mode. In both analyses, mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in methanol. The chromatographic separation of analytes was performed with gradient elution of increasing mobile phase B (0% hold until 0.7 minutes, 0–15% from 0.7–1 minute, 15–100% from 1–4 minutes, 100% hold from 4–4.5 minutes, 0% from 4.5–6 minutes for positive mode; 0% hold until 0.7 minutes, 0–100% from 0.7–2.5 minutes, 100% hold from 2.5–3.5 minutes, 0% from 3.5–5 minutes for negative mode). Flow was diverted to waste for the first 0.7 minutes and after 4 minutes. Total run time was 6 and 5 minutes for positive and negative mode, respectively.

MS/MS analysis was performed on a triple quadrupole mass spectrometer API 4000 (Applied Biosystems–ABSciex, Foster City, CA, USA) operated with electrospray ionization (TurboV source using the electrospray probe). Ionspray voltage and turbo heater temperature were kept at 2500 V (-2000 V for tazobactam) and 500° C, respectively. Compound-specific

instrument parameters were optimized for each transition (Table 1.2) to obtain the most robust signal.

#### *Linearity, limit of quantification, and limit of detection*

Linearity was assessed using 5 calibration curves analyzed on separate days. For validation, each point on the calibration curve was run in duplicate (2 separate extractions), and the curves were constructed by calculating the peak area ratios of each compound to the internal standard and plotting these against the nominal concentration of the sample. Back-calculated calibration concentrations were determined using several models. The calibration curve with the best accuracy and precision throughout the curve range was considered the best fit. Quadratic regression of the ratio of compound to internal standard concentration (x) versus peak area ratio of compound to internal standard (y) using a  $1/(x)$  weighting scheme was used for calculations because it provided the best fit to the data.

The upper limit of quantification (ULOQ) was defined as the highest standard concentration for which both the relative standard deviation and the percent deviation from the nominal concentration were less than 15%.<sup>8</sup> The lower limit of quantification (LLOQ) was defined as the lowest concentration for which both the relative standard deviation and the percent deviation from the nominal concentration were less than 20%. The detection limit was defined as signal to noise ratio of 3:1.

#### *Matrix effects*

Seven different lots from 2 separate plasma matrices (2 lots sodium heparin and 5 lots potassium triphosphate EDTA) were spiked in triplicate, extracted, and analyzed as separate

samples. The following compound concentrations were tested: 18,000 ng/mL for ampicillin, piperacillin, and tazobactam; 6,000 ng/mL for meropenem and acyclovir; and 3,000 ng/mL for metronidazole. Calculated concentrations for each extracted lot were compared to theoretical concentrations. In addition, the method's specificity was tested by screening the 7 different human blank plasma lots for drugs and internal standard.

*Accuracy, precision, and recovery (extraction efficiency)*

Accuracy and precision of the analytical method was quantified using 4 concentrations of QC samples (including LLOQ) run 6 times (6 separate extractions) in sequence on 5 different days (total of 30 replicates for each concentration). In addition, accuracy and precision of diluted samples were determined. Dilutions (1:1, 1:3, and 1:9 ratios) of a highly concentrated solution (300,000 ng/mL for ampicillin, piperacillin, and tazobactam; 100,000 ng/mL for meropenem and acyclovir; and 50,000 ng/mL for metronidazole) were performed with human plasma. The calculated concentrations were compared to the nominal concentrations.

Recovery (extraction efficiency) of the 6 compounds was determined with QC samples (all 3 QC concentration levels) by dividing the peak area of the extracted spiked plasma samples with the peak area of a spiked blank plasma extract.

*Stability*

To test stability, samples were left at room temperature for 24 hours prior to extraction. Stability during sample handling was also verified by subjecting samples to either 3 freeze-thaw cycles or storage for 24 hours in the refrigerator at 4° C prior to extraction. QC

samples at the 3 concentrations were used for this purpose. Also, stability in the autosampler for 24 hours was tested. One-month stability was tested by storing aliquots of QC samples for 1 month in the -80° C freezer.

## Results

### *Linearity*

The calibration curve was calculated using peak area ratio values at 7 standard concentrations. A quadratic regression provided the best fit to the data. The data for the calibration curves (n=5) are shown in Table 1.3, along with the mean  $\pm$  standard deviation of 5 standard curve quadratic coefficients, slopes, intercepts, and correlation coefficients ( $r^2$ ). The regression coefficient ( $r^2$ ) for all calibration curves was greater than 0.9965. Due to day-to-day variations in the coefficients of the quadratic equation, standards and QCs should be generated for each day of analysis.

### *Matrix effect*

The percent difference from theoretical concentrations for all analytes was less than 15%, except for acyclovir (21% difference, lot #1) and meropenem (26% difference, lot #3) (Table 1.4). Therefore, the extraction method was suitable for all analytes spiked in these matrices, except for the lots mentioned above. In addition, no response in MS/MS channels used for monitoring both drugs and internal standards was observed in any of the 7 human plasma lots.

### *The limit of quantification*

The LLOQ for ampicillin, piperacillin, tazobactam, metronidazole, meropenem, and acyclovir were 300, 300, 150, 50, 100, and 100 ng/mL, respectively, and the ULOQ for ampicillin, piperacillin, tazobactam, metronidazole, meropenem, and acyclovir were 150,000, 150,000, 75,000, 25,000, 50,000, and 50,000 ng/mL, respectively. Chromatograms of blank, LLOQ, and ULOQ samples are shown in Fig. 1.1 and Fig. 1.2.

### *Accuracy, precision, and recovery*

The results of the accuracy and precision experiments at 4 different quality control levels are shown in Table 1.5. Within-day accuracy of all analytes ranged from 85–110%, with a mean of 101%. Between-day accuracy of all analytes ranged from 92–110%, with a mean of 101%. Within- and between-day coefficient of variations varied from 2.1–11.4%, and 4.0–9.1%, respectively. Overall, results indicate that the method was accurate and precise for each compound. In addition, concentration measurements of partially diluted samples were accurate and precise across all dilution ratios. The greatest percent deviation for all diluted samples was 16.8% for metronidazole when diluted 1:9. The greatest percent coefficient of variation for all the diluted samples was 14.1%. The absolute recovery of all compounds at all concentrations was greater than 75% (Table 1.3).

### *Stability*

Overall, each compound was stable under most tested conditions, with a few exceptions. After 24 hours at room temperature, all compound concentrations were within 15% of nominal, with the exception of tazobactam (82% of nominal), piperacillin (75%), and

meropenem (84%). In 3 freeze-thaw cycles, on average all compound concentrations were within 10% of nominal. The low QC for ampicillin deviated 16% from nominal. All compounds were stable when left in the autosampler for 24 hours at 8° C (within 12% of nominal concentration), and all compounds were stable when left in the refrigerator (4° C) for 24 hours, being within 13% of the nominal concentration. In addition, after 1 month of storage at <70° C, all compounds were within 15% of controls.

#### *Analysis of patient samples*

We evaluated the applicability of the described method by analyzing sparse plasma samples collected from premature infants (<32 weeks gestational age at birth, N=8) given multiple intravenous doses of piperacillin-tazobactam (Table 1.6). Piperacillin and tazobactam were found in almost all patient samples. The mean (standard deviation [SD]) estimated gestational age at birth, postnatal age, and birth weight were 25 (2.7) weeks, 7 (7) days, and 728 (185) grams, respectively. The overall mean (SD) piperacillin concentration was 41,123 (53,789) ng/mL; the mean (SD) piperacillin concentration in infants < and ≥ 28 weeks postmenstrual age were 45,159 (58,686, n=6) and 24,310 (20,186, n=2) ng/mL, respectively. In addition to piperacillin and tazobactam, ampicillin was found in 5 patients, metronidazole in 3 patients, and acyclovir in 1 patient. Meropenem was not found in any of the samples. Dosing of these agents could be confirmed in 7/8 patients.

#### Discussion

The method described in this report measures drug concentration of 6 antimicrobials accurately and precisely in micro-volumes (50 µL) of plasma. Previous investigators have



developed analytical methods to measure drug concentrations of antimicrobials in low plasma volumes; however, most involve antimicrobials of the same drug class and no antivirals.<sup>4</sup> The ability to simultaneously measure drug concentrations of antimicrobials from different classes, including antivirals, is an important milestone in evaluating drug disposition in premature infants. The latter is often challenging due to blood volume limitations in this population; therefore, drug concentration information obtained from each sample should be maximized. This can be accomplished with this assay as premature infants are often treated with several antimicrobials simultaneously. This is evidenced in the patient samples tested, as acyclovir and metronidazole were found in some of the infants treated with piperacillin-tazobactam. A high degree of variability and a trend towards decreasing piperacillin concentrations was observed with increasing postmenstrual age. Even though it is not possible to perform formal statistical inferences to assess significance of piperacillin concentration differences between postmenstrual age groups, it is likely that these differences result from maturational changes characteristic of the developing infant. These developmental changes are often related to improvement in renal function that leads to increased piperacillin clearance. This observation has been demonstrated in previous studies evaluating the PK of piperacillin in more mature premature infants.<sup>9</sup> A formal population PK analysis is underway to quantify and identify sources of variability in piperacillin concentrations in this population.

In addition to the advantages offered by micro-volumes and multiplex methodologies in premature infant studies, dried blood spot (DBS) sampling is becoming an attractive technology for use in this population. This technology requires minimum amounts of whole blood per sample (<30  $\mu$ L), virtually no sample processing, and convenient room

temperature storage. Even though several bioanalytical assays have been developed using DBS technology, only 1 clinical study has evaluated the use of DBS in premature infants.<sup>10</sup> The utility of this technology across therapeutics in this population remains to be determined.

The extraction process (protein precipitation) used for this method has been previously described for beta-lactam antibiotics.<sup>4</sup> In the present method, this simple and straightforward extraction process provided excellent recovery (>90%) for most compounds. It is possible that the compounds with the lowest extraction efficiency (77–83%), meropenem and acyclovir, remained trapped in the protein precipitate or did not completely dissolve into the organic phase. In spite of this limitation, the extraction procedure used in this method provides a high level of efficiency in sample preparation, as well as high throughput processing of patient samples.

Although clinical plasma samples >50 µL from premature infants can be obtained, it is not without difficulty. This assay was designed to use sample volumes as low as 5 µL, which holds a number of advantages. Samples requiring repeat analysis can be diluted (1:1, 1:3, or 1:9) with blank plasma and extracted. This is particularly advantageous for concentrations >ULOQ that need to be diluted back into the curve. Samples known to contain beta-lactams (tazobactam, piperacillin, meropenem) should be handled carefully given the lack of stability of these compounds at room temperature. Freeze-thaw cycles, however, did not affect the stability of any of the compounds, which allows for retesting of samples if needed.

We successfully developed a method to simultaneously assay ampicillin, piperacillin, tazobactam, meropenem, acyclovir, and metronidazole in human plasma. The assay has been validated with respect to accuracy, precision, limit of detection, recovery, and stability

(except as noted). The assay has been successfully applied to clinical samples from premature infants. This method has many clinical applications within the field of pediatrics, as it is simple, highly sensitive and specific, and requires micro-volumes of sample.

## References

1. Stoll BJ, Hansen N, Fanaroff SS, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110 (2 Pt 1):285–291.
2. Stoll BJ, Hansen NI, Higgins RD, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002–2003. *Pediatr Infect Dis J*. 2005;24(7):635–639.
3. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics*. 2006;117(6):1979–1987.
4. Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA. Microanalysis of beta-lactam antibiotics and vancomycin in plasma for pharmacokinetic studies in neonates. *Antimicrob Agents Chemother*. 2009;53(1):75–80.
5. Jung BH, Rezk NL, Bridges AS, Corbett AH, Kashuba AD. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. *Biomed Chromatogr*. 2007;21(10):1095–1104.
6. Denooz R, Charlier C. Simultaneous determination of five beta-lactam antibiotics (cefepim, ceftazidim, cefuroxim, meropenem and piperacillin) in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2008;864(1-2):161–167.
7. Holt DE, de Louvois J, Hurley R, Harvey D. A high performance liquid chromatography system for the simultaneous assay of some antibiotics commonly found in combination in clinical samples. *J Antimicrob Chemother*. 1990;26(1):107–115.
8. Shah VP, Midha KK, Findlay JW, et al. Bioanalytical method validation--a revisit with a decade of progress. *Pharm Res*. 2000;17(12):1551–1557.
9. Kacet N, Roussel-Delvallez M, Gremillet C, Dubos JP, Storme L, Lequien P. Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. *Pediatr Infect Dis J*. 1992;11(5):365–369.
10. Suyagh M, Collier PS, Millership JS, et al. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. *Pediatrics*. 2011;127(2):e367–374.

Table 1.1. Individual stock solutions

Compound	Desired concentration (mg/mL)	Amount (mg) <sup>a</sup>	Diluent amount (DMSO) (mL)
Ampicillin	15	16.0	1
Piperacillin	15	15.7	1
Tazobactam	15	16.2	1
Meropenem	5	5.8	1
Acyclovir	5	5.0	1
Metronidazole	2.5	2.5	1

<sup>a</sup>Corrected for salt weight where applicable. DMSO: dimethyl sulfoxide.

Table 1.2. Optimal precursor and product ions and instrument parameters by compound

	Molecular weight (g/mol)	Ionization mode	Precursor ion	Product ion	Collision gas	Collision energy (eV)
Ampicillin	349.40	Positive	350.1	160.1	10	20
Piperacillin	517.55	Positive	518.2	143.2	10	25
Tazobactam	300.29	Negative	299.0	137.9	10	-20
Meropenem	383.46	Positive	384.1	141.1	10	25
Acyclovir	225.20	Positive	226.1	152.1	10	18
Metronidazole	171.153	Positive	172.1	128.1	10	20
Dicloxacillin (IS)	470.32	Positive	470.1	160.1	10	20
Dicloxacillin (IS)	470.32	Negative	468.0	326.8	10	-20

IS: internal standard.

Table 1.3. Summary of standard curve, retention times, and extraction efficiency

Compound	Range ng/mL	r <sup>2</sup>	Quadratic			Slope	SD	Intercept	SD	Retention time min	Extraction efficiency %	Mean deviation %
			coefficient	SD	SD							
Ampicillin	300–150,000	0.9981	-1.6842E-10	1.9132E-10	2.3660E-04	7.4519E-05	-5.4400E-02	1.7704E-02	1.76	97.33	0.10	
Piperacillin	300–150,000	0.9984	-1.3646E-09	5.2397E-10	7.2780E-04	1.9669E-04	-8.1600E-02	1.5208E-02	2.32	97.66	0.03	
Tazobactam	150–75,000	0.9986	-4.3600E-10	5.4385E-11	1.5160E-04	2.0748E-05	-4.1740E-04	2.5241E-03	2.61	94.66	0.20	
Meropenem	100–50,000	0.9974	-4.8644E-11	1.4345E-10	1.7510E-04	5.3558E-05	-3.0180E-02	8.3174E-03	1.72	77.33	0.70	
Acyclovir	100–50,000	0.9966	-5.4780E-10	2.7185E-10	3.3120E-04	5.7160E-05	-1.8948E-02	1.4136E-02	1.59	83.00	1.40	
Metromidazole	50–25,000	0.9972	-1.5890E-09	2.3465E-09	6.9140E-04	6.6114E-04	-1.4320E-02	1.7062E-02	1.77	97.66	0.10	
Diloxacillin (IS)									2.82	92.24		

IS: internal standard; SD: standard deviation.

Table 1.4. Matrix effects

<i>Lot #</i>	Plasma matrix						
	K3 EDTA	K3 EDTA	K3 EDTA	K3 EDTA	K3 EDTA	Sodium heparin	Sodium heparin
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>1</i>	<i>2</i>
<b>Ampicillin</b>							
Mean concentration (ng/mL)	20,567	18,833	20,133	19,367	18,567	18,533	17,833
% deviation	14.26	4.63	11.85	7.59	3.15	2.96	-0.93
<b>Piperacillin</b>							
Mean concentration (ng/mL)	18,733	17,667	18,333	17,733	19,567	17,633	17,467
% deviation	4.07	-1.85	1.85	-1.48	8.70	-2.04	-2.96
<b>Tazobactam</b>							
Mean concentration (ng/mL)	18,133	18,933	18,300	19,000	17,767	17,500	18,133
% deviation	0.74	5.19	1.67	5.56	-1.30	-2.78	0.74
<b>Meropenem</b>							
Mean concentration (ng/mL)	6,722	5,989	7,533	6,233	6,353	5,511	5,756
% deviation	12.04	-0.19	25.56	3.89	5.89	-8.15	-4.07
<b>Acyclovir</b>							
Mean concentration (ng/mL)	7,289	6,089	6,756	6,189	6,927	6,444	6,056
% deviation	21.48	1.48	12.59	3.15	15.44	7.41	0.93
<b>Metronidazole</b>							
Mean	3,261	3,228	3,222	3,144	3,250	3,089	3,011



Plasma matrix							
	K3 EDTA	K3 EDTA	K3 EDTA	K3 EDTA	K3 EDTA	Sodium heparin	Sodium heparin
<i>Lot #</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>1</i>	<i>2</i>
concentration (ng/mL)							
% deviation	8.70	7.59	7.41	4.81	8.33	2.96	0.37

K3 EDTA: potassium triphosphate ethylenediaminetetraacetic acid.

Table 1.5. Summary of accuracy and precision

Compound	Concentration (ng/mL)	Intra-assay		Inter-assay	
		Accuracy (%)	CV (%)	Accuracy (%)	CV (%)
Ampicillin	300	100.33	4.36	101.49	6.18
	900	96.29	5.20	95.37	6.97
	60,000	107.01	2.85	106.62	3.98
	120,000	98.00	4.03	98.19	5.26
Piperacillin	300	107.69	2.99	107.94	6.35
	900	99.00	5.43	99.54	6.49
	60,000	102.82	3.72	103.82	5.65
	120,000	100.64	7.04	101.25	8.20
Tazobactam	150	98.09	4.63	99.16	6.75
	450	110.39	4.32	109.53	5.38
	18,000	104.24	2.63	104.54	5.42
	60,000	99.71	2.29	99.66	7.02
Meropenem	100	101.96	5.40	103.23	7.81
	300	94.10	5.91	94.99	7.50
	20,000	107.59	3.22	107.63	4.22
	40,000	99.22	4.65	99.58	6.07
Acyclovir	100	100.78	5.73	100.31	9.06
	300	92.17	5.51	92.43	7.96
	20,000	92.64	4.31	92.72	6.01
	40,000	92.03	6.88	93.44	8.50
Metronidazole	50	102.78	8.42	101.29	9.44
	150	95.24	6.64	96.05	7.73
	10,000	106.31	4.03	107.10	6.11
	20,000	100.08	4.09	100.08	6.62
Mean		100.38	4.76	100.67	6.70

CV: coefficient of variation.

Table 1.6. Drug concentrations in patient samples

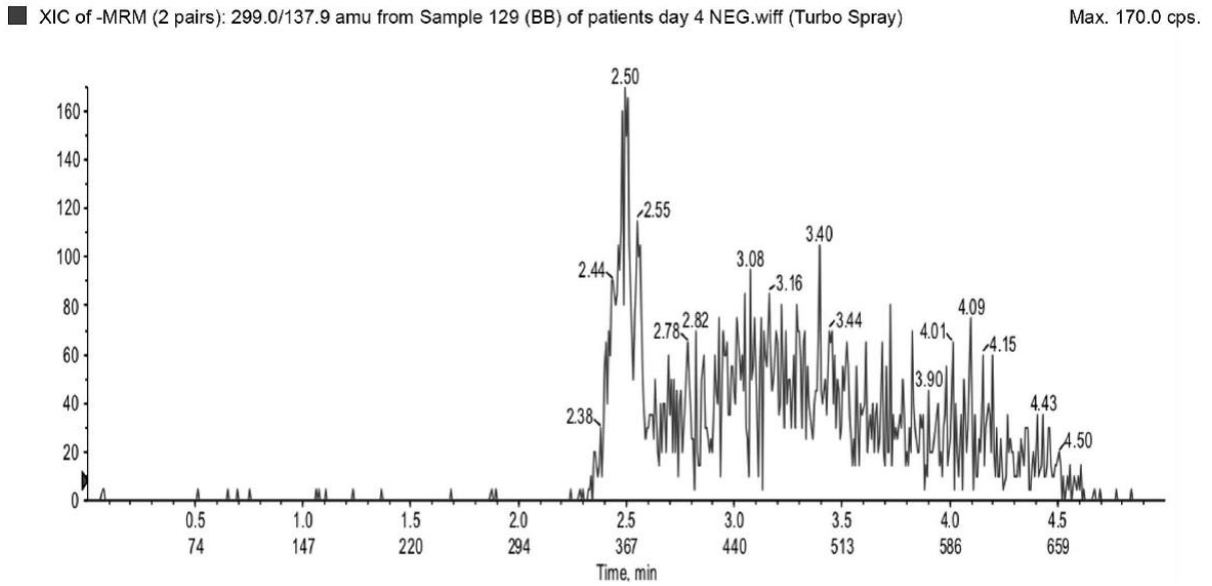
Subject ID	Sample no.	Piperacillin ng/mL	Tazobactam ng/mL	Ampicillin ng/mL	Meropenem ng/mL	Acyclovir ng/mL	Metronidazole ng/mL
1	1	28200	1260	346	BLD	BLD	BLD
1	2	49850	2725	BLD	BLD	BLD	BLD
1	3	48000	2820	438	BLD	BLD	BLD
2	1	24300	2730	BLD	BLD	BLD	BLD
2	2	53400	6800	BLQ	BLD	BLD	BLD
3	1	42600	7290	55400	BLD	BLD	BLD
4	1	52000	16200	3330	BLD	BLD	13700
4	2	47300	11900	23100	BLD	BLD	21800
4	3	BLD	BLD	BLQ	BLD	BLD	BLD
4	4	BLD	BLD	BLD	BLD	BLD	BLD
4	5	32750	6450	BLD	BLD	BLD	7050
4	6	85600	15480	602	BLD	BLD	8000
4	7	37500	7720	BLD	BLD	BLD	1060
5	1	3640	BLQ	BLQ	BLQ	BLD	BLD
5	2	4920	BLQ	BLQ	BLD	BLD	352
5	3	17000	851	BLQ	BLD	BLD	87.3
6	1	78100	10300	374000	BLD	BLD	BLD
6	2	286000	19900	367000	BLD	BLD	BLD
6	3	64400	11400	532000	BLQ	BLD	BLD
7	1	69900	8760	145000	BLD	BLD	BLD
7	2	111000	10400	78800	BLQ	BLD	BLD
7	3	54400	6360	355000	BLD	BLD	BLD
7	4	20900	2450	88600	BLD	BLD	BLD
7	5	18100	2740	460000	BLD	BLD	BLD
7	6	11850	BLD	94000	BLD	BLD	BLD
7	7	6760	1250	427000	BLD	BLD	BLD
8	1	6990	BLQ	BLD	BLD	51800	BLD
8	2	1890	BLD	BLD	BLD	9140	BLD
8	3	1940	BLD	BLD	BLD	85300	BLD
8	4	1830	BLD	BLD	BLD	3610	1110

Subject ID	Sample no.	Piperacillin ng/mL	Tazobactam ng/mL	Ampicillin ng/mL	Meropenem ng/mL	Acyclovir ng/mL	Metronidazole ng/mL
8	5	5760	BLD	BLD	BLD	21900	BLD
8	6	7490	BLQ	BLD	BLD	35500	BLD
8	7	BLD	BLD	BLD	BLD	10100	BLD
8	8	BLQ	BLD	BLD	BLD	3110	BLD
8	9	BLQ	BLD	BLD	BLD	1310	79.2
8	10	460	BLD	BLD	BLD	1200	91.4

BLD: below the level of detection; BLQ: below the level of quantification.

Fig. 1.1. Blank plasma sample run in a) negative (tazobactam) and b) positive (top to bottom: metronidazole, acyclovir, ampicillin, meropenem, piperacillin) ionization mode.

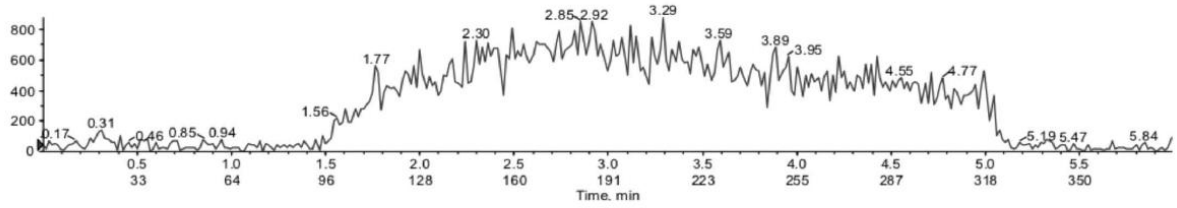
A.



B.

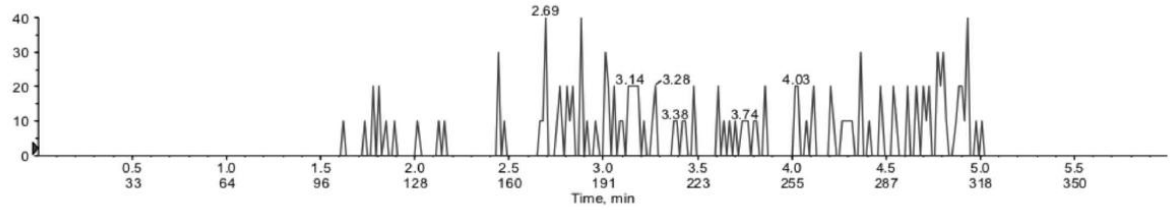
■ XIC of +MRM (9 pairs): 172.1/128.1 amu from Sample 1 (BB) of patients day 4 POS.wiff (Turbo Spray)

Max. 880.0 cps.



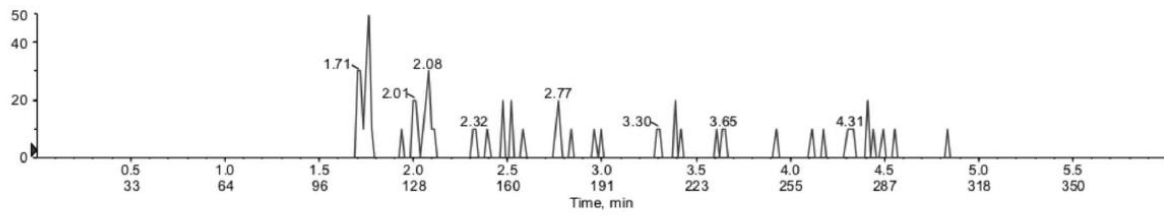
■ XIC of +MRM (9 pairs): 226.1/152.1 amu from Sample 1 (BB) of patients day 4 POS.wiff (Turbo Spray)

Max. 40.0 cps.



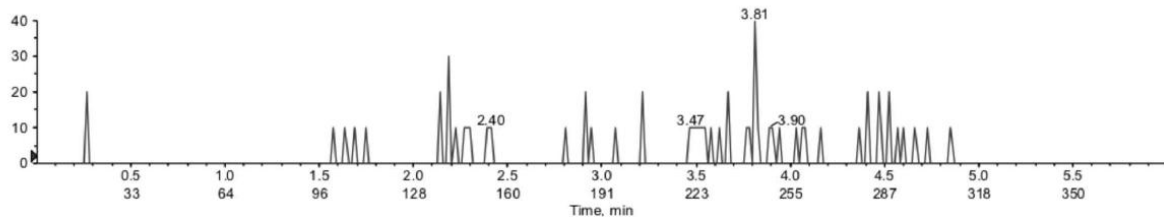
■ XIC of +MRM (9 pairs): 350.1/160.1 amu from Sample 1 (BB) of patients day 4 POS.wiff (Turbo Spray)

Max. 50.0 cps.



■ XIC of +MRM (9 pairs): 384.1/141.1 amu from Sample 1 (BB) of patients day 4 POS.wiff (Turbo Spray)

Max. 40.0 cps.



■ XIC of +MRM (9 pairs): 518.2/143.3 amu from Sample 1 (BB) of patients day 4 POS.wiff (Turbo Spray)

Max. 530.0 cps.

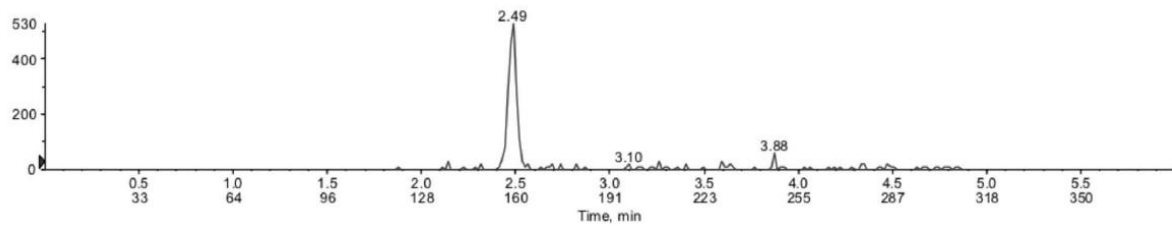
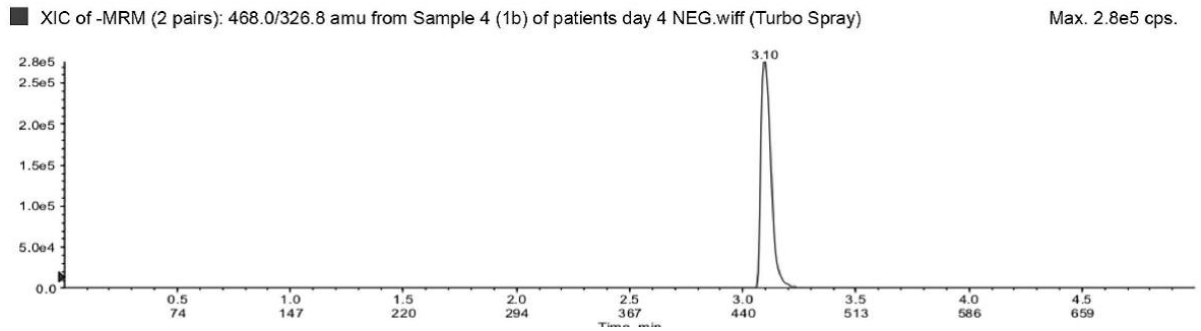
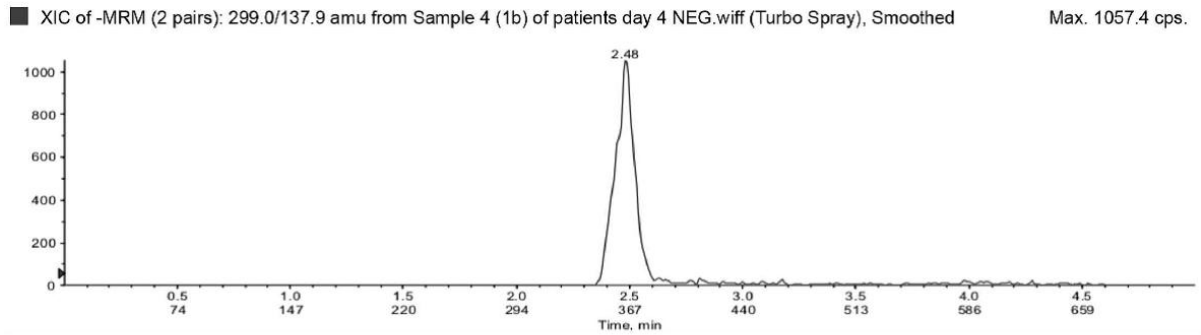


Fig. 1.2. Lower limit of quantification in a) negative (top to bottom: tazobactam and dicloxacillin [IS]) and b) positive (top to bottom: dicloxacillin [IS], metronidazole, acyclovir, ampicillin, meropenem, piperacillin) ionization mode. Upper limit of quantification in c) negative (top to bottom: tazobactam and dicloxacillin [IS]) and d) positive (top to bottom: dicloxacillin [IS], metronidazole, acyclovir, ampicillin, meropenem, piperacillin) ionization mode. IS: internal standard.

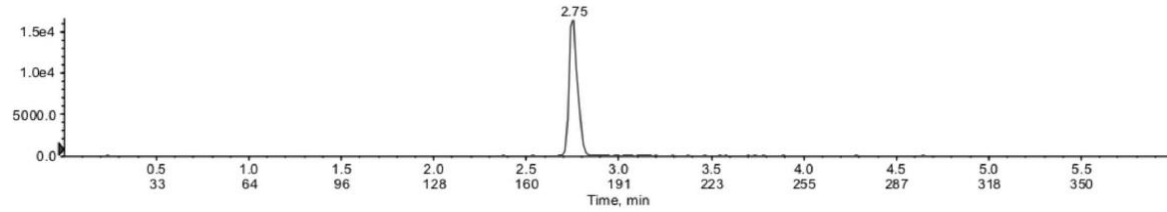
A.



B.

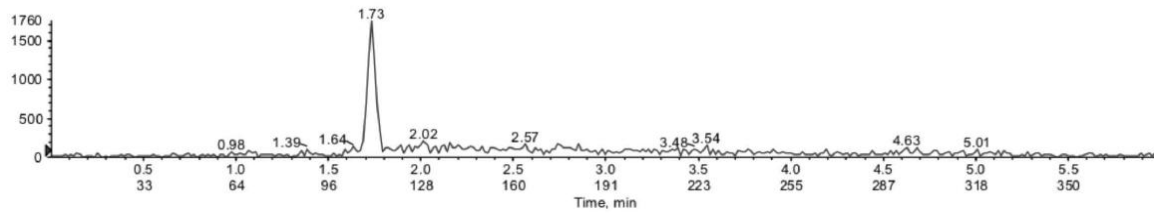
■ XIC of +MRM (9 pairs): 470.1/160.1 amu from Sample 129 (1a) of patients day 4 POS.wiff (Turbo Spray)

Max. 1.7e4 cps.



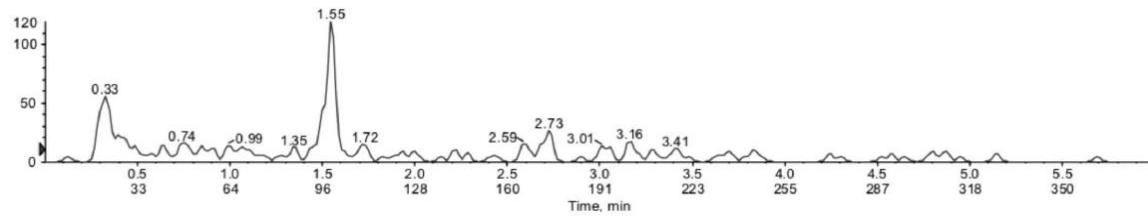
■ XIC of +MRM (9 pairs): 172.1/128.1 amu from Sample 129 (1a) of patients day 4 POS.wiff (Turbo Spray)

Max. 1760.0 cps.



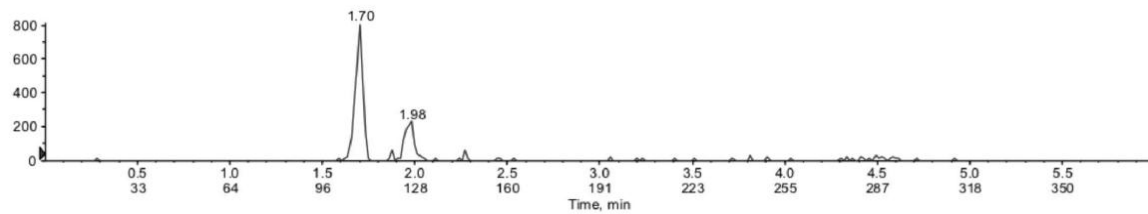
■ XIC of +MRM (9 pairs): 226.1/152.1 amu from Sample 129 (1a) of patients day 4 POS.wiff (Turbo Spray), Smoothed

Max. 119.5 cps.



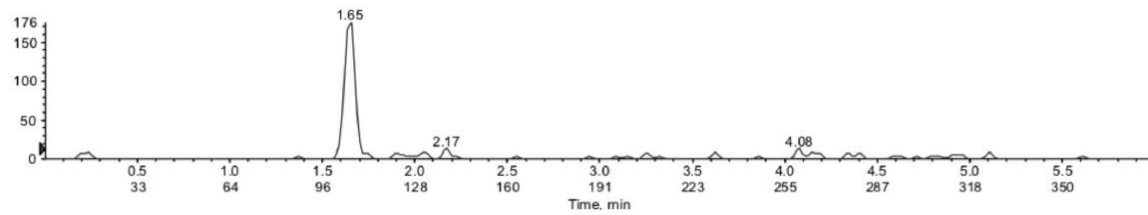
■ XIC of +MRM (9 pairs): 350.1/160.1 amu from Sample 129 (1a) of patients day 4 POS.wiff (Turbo Spray)

Max. 810.0 cps.



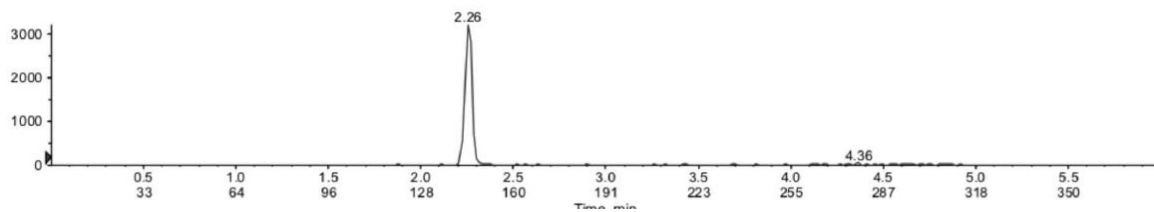
■ XIC of +MRM (9 pairs): 384.1/141.1 amu from Sample 129 (1a) of patients day 4 POS.wiff (Turbo Spray), Smoothed

Max. 176.1 cps.



■ XIC of +MRM (9 pairs): 518.2/143.3 amu from Sample 129 (1a) of patients day 4 POS.wiff (Turbo Spray)

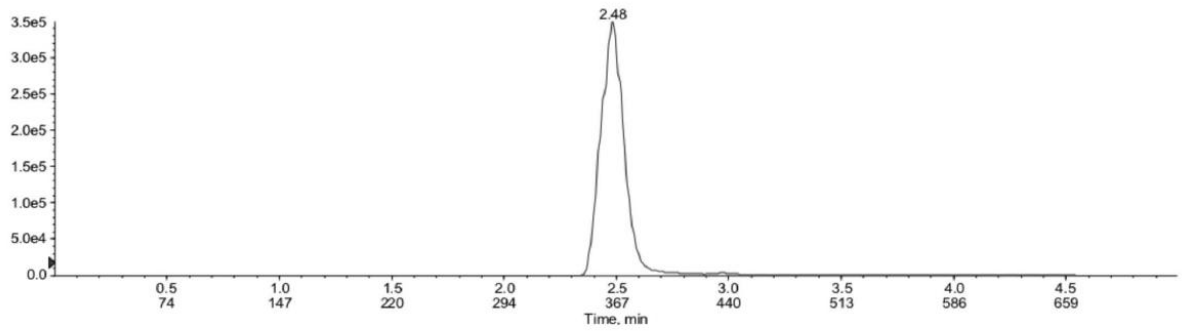
Max. 3200.0 cps.



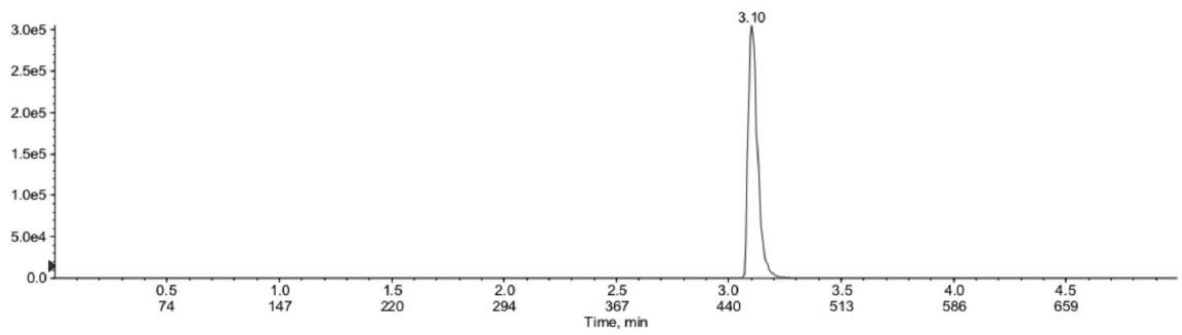


C.

■ XIC of -MRM (2 pairs): 299.0/137.9 amu from Sample 15 (S6) of patients day 4 NEG.wiff (Turbo Spray), Smoothed Max. 3.5e5 cps.



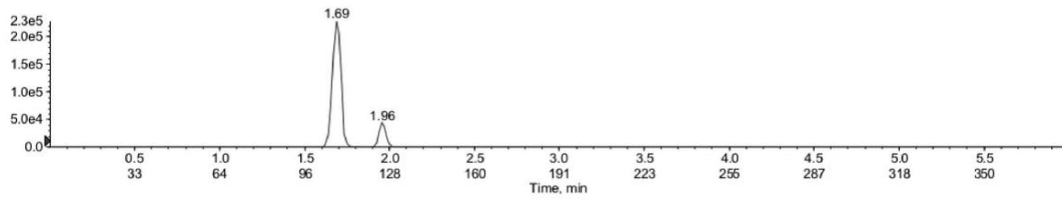
■ XIC of -MRM (2 pairs): 468.0/326.8 amu from Sample 15 (S6) of patients day 4 NEG.wiff (Turbo Spray) Max. 3.1e5 cps.



D.

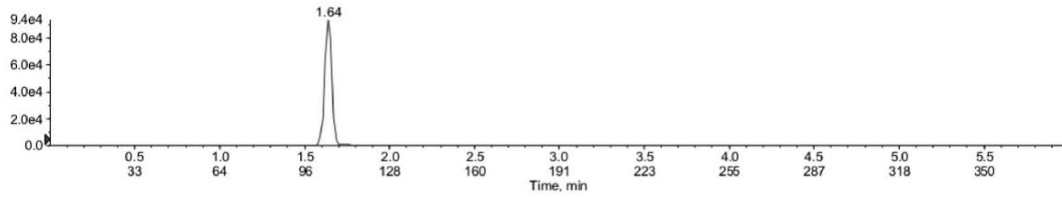
■ XIC of +MRM (9 pairs): 350.1/160.1 amu from Sample 142 (S7) of patients day 4 POS.wiff (Turbo Spray)

Max. 2.3e5 cps.



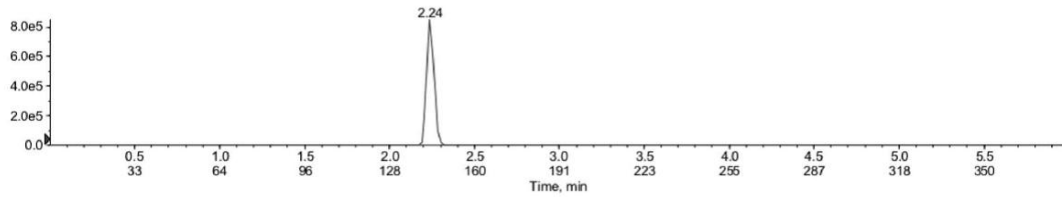
■ XIC of +MRM (9 pairs): 384.1/141.1 amu from Sample 142 (S7) of patients day 4 POS.wiff (Turbo Spray)

Max. 9.4e4 cps.



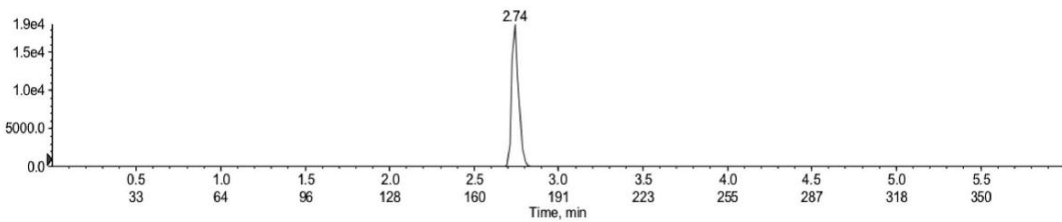
■ XIC of +MRM (9 pairs): 518.2/143.3 amu from Sample 142 (S7) of patients day 4 POS.wiff (Turbo Spray)

Max. 8.5e5 cps.



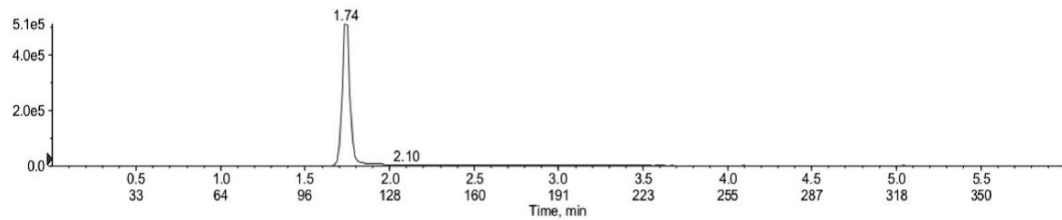
■ XIC of +MRM (9 pairs): 470.1/160.1 amu from Sample 141 (S7) of patients day 4 POS.wiff (Turbo Spray)

Max. 1.9e4 cps.



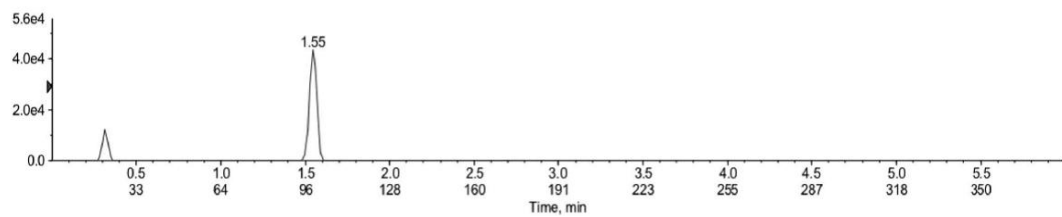
■ XIC of +MRM (9 pairs): 172.1/128.1 amu from Sample 141 (S7) of patients day 4 POS.wiff (Turbo Spray)

Max. 5.1e5 cps.



■ XIC of +MRM (9 pairs): 226.1/152.1 amu from Sample 141 (S7) of patients day 4 POS.wiff (Turbo Spray)

Max. 4.4e4 cps.



## CHAPTER II: POPULATION PHARMACOKINETICS OF PIPERACILLIN USING SCAVENGED SAMPLES FROM PRETERM INFANTS

### Introduction

Piperacillin is a semisynthetic derivative of ampicillin with a ureido and piperazine side chain.<sup>1</sup> The combination of piperacillin with tazobactam (beta-lactamase inhibitor) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of children >2 months of age with appendicitis or peritonitis. The European Medicines Agency has approved the combination for the treatment of complicated intra-abdominal infections in children 2–12 years of age. Safety, efficacy, and dosing recommendations for infants <2 month of age have not been established. In adults and older children, more than 70% of piperacillin is primarily excreted unchanged in the urine. Total body clearance increases and elimination half-life decreases with increasing age.<sup>2,3</sup> After intravenous administration, the elimination half-life of piperacillin in adults and children 2–12 years of age is short (0.5–1 hour); elimination half-life is prolonged in children and infants <23 months of age (0.9–1.4 hours).<sup>2,3</sup>

In infants <2 months of age, piperacillin-tazobactam is commonly used “off label” for the treatment of intra-abdominal infections, such as necrotizing enterocolitis, as well as severe infections due to bacterial resistance. Appropriate dosing recommendations for this population have been limited by single-center studies and exclusion of the most preterm (<28 weeks gestational age at birth) infants.<sup>4</sup> Because the main clearance mechanism for

piperacillin is the renal system, ontogenic pharmacokinetic (PK) changes in the developing infant are expected. Extrapolation of PK data from more mature infants is often difficult due to non-linear relationships between maturation and renal function.<sup>5</sup> PK studies are needed in preterm infants to appropriately describe drug disposition in this population.

PK studies are rarely conducted in infants due to the research challenges posed by this population in the context of traditional study design. These challenges include limited blood volume for PK sampling, difficulty in obtaining PK samples due to the critical medical condition of the infants, and low parental informed consent rates. As such, investigators have explored novel minimal-risk methods to evaluate the PK of antimicrobials in this population. One approach is the use of scavenged samples, left over from the normal clinical care of infants. When combined with the collection of timed PK samples (collected specifically for study purposes), scavenged samples have allowed for characterization of the PK in preterm infants.<sup>6</sup> To our knowledge, the use of scavenged samples for PK analysis of other antimicrobials has not been evaluated. The present study was conducted to assess the population PK of intravenous piperacillin using scavenged samples collected from preterm infants <32 weeks gestational age at birth.

## Methods

### *Study design*

Pharmacokinetic samples for this analysis were obtained from the Antimicrobial PK in High-Risk Infants trial sponsored by the Pediatric Pharmacology Research Unit. This multi-center, prospective, open-label PK study of commonly used antimicrobial agents in the neonatal intensive care unit enrolled infants  $\leq 32$  weeks gestational age at birth who were

<120 days old and who were receiving intravenous piperacillin or piperacillin-tazobactam per routine medical care. Piperacillin dosing was determined by the routine clinical practice in each unit, and no exclusion criteria were used. Infants were stratified by birth gestational age (BGA) at enrollment: <26 weeks, 26–29 weeks, and 30–32 weeks. The study was approved by the institutional review boards at each institution, and informed consent was obtained prior to enrollment.

The following information was collected for covariate analysis: BGA, postnatal age (PNA), postmenstrual age (PMA), weight, sex, race, serum creatinine, and ethnicity. Covariates that exhibited time-dependent changes (e.g., weight, PNA) were permitted to change with time, and the actual value in the data set reflects the observations made at each patient visit. Missing weights were imputed with the last recorded value carried forward for up to 7 days. Serum creatinine (SCR) was recorded when obtained for clinical care. Missing SCR values were imputed based on an exponential model of SCR and PMA derived from the data.

#### *PK sample collection*

A sparse sampling approach was followed in this study. Samples were divided into 2 types: scavenged and blood draw. *Scavenged samples* were defined as samples obtained without obtaining additional blood from the infant. These samples were collected from the clinical laboratory from discarded blood (heparinized or ethylenediaminetetraacetic acid [EDTA] tubes) obtained for routine clinical care. *Blood draw samples* were defined as samples obtained with collection of extra blood from the infant. Each blood draw was approximately 0.3 mL of blood collected in EDTA Microtainers. PK sample collection was

planned at the following time points: immediately prior to piperacillin infusion, immediately after the completion of infusion (t=0), approximately 1 hour after completion of infusion (t=1 hour), approximately 2 hours after completion of infusion (t=2 hours), and immediately prior to infusion of the next dose. The duration of piperacillin infusion was performed according to routine clinical care at the site. Samples were refrigerated or placed on ice immediately after collection and then centrifuged at 1500 g and 4° C for 10 minutes. Plasma was removed and stored at -70° C. Samples from all sites were shipped on dry ice to Duke University Medical Center where they were stored at -70° C prior to analysis. Samples were stored for a maximum of 32 months prior to analysis.

#### *Bioanalytical assay*

A liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) assay for piperacillin detection in human plasma suitable for small plasma volumes was developed and validated. Sample analysis was performed on a triple quadrupole mass spectrometer API 4000 (Applied Biosystems–ABSciex, Foster City, CA, USA) operated with electrospray ionization (TurboV source using a TurboIonspray® probe). Instrument parameters were optimized for the piperacillin transition (518.2→143.2 m/z). Ionspray voltage and turbo heater temperature were kept at 2500 V and 500° C, respectively; a collision gas of 10 and a collision energy of 25 V were used. Piperacillin and dicloxacillin (internal standard [IS]) were purchased from the Sigma Chemical Company (St. Louis, MO, USA). HPLC separation was achieved using a reverse-phase C18 Aquasil column (Thermo Fisher, Waltham, MA, USA) with a flow-rate of 0.75 ml/min using a gradient mobile phase. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in

methanol. Total run time was 6 minutes. Analytical data were acquired by Analyst Software 1.4.1 (Applied Biosystems–ABSciex, Foster City, CA, USA). The lower limit of quantitation of piperacillin in plasma was 0.3 mg/L. Intraday and interday coefficients of variation were <7% at concentrations ranging from 0.3–120 mg/L.

### *Population PK analysis*

PK data were analyzed with a nonlinear mixed effect modeling (NONMEM) approach using the computer program NONMEM (version 7) in conjunction with WINGS for NONMEM version 7.03 (Auckland, NZ). Output was summarized using STATA 10 (College Station, TX, USA). The first-order conditional estimation method with interaction was used for all model runs. One- and 2-compartment structural PK models were evaluated. Inter-individual (IIV) random effects were evaluated on clearance (CL) and volume of distribution (V). Covariance was described by a block Omega matrix. An exponential model for IIV variance for CL and V was used, and a proportional error model was deemed appropriate to describe residual variability. The potential impact of clinical covariates on PK parameters was explored if a relationship was suggested by visual inspection of scatter and box plots (continuous and categorical variables, respectively) of individual Bayesian estimates obtained from the base model and IIV (ETAs) against covariates. The following covariates were evaluated: weight (kg), BGA (weeks), PNA (days), PMA (defined as BGA plus PNA in weeks [PNA/7]), SCR, race, sex, and ethnicity. Once covariates were identified during the model-building process, covariate testing was performed via standard forward addition backward elimination methods. Potential covariates that reduced the objective function by more than 3.84 ( $P < \sim 0.05$ ) were included in the subsequent multivariable

analysis. A forward inclusion with backwards elimination approach was used during the multivariable step, and a reduction of 6.63 ( $P < \sim 0.01$ ) was required for retention of a covariate in the final model. Continuous covariates were scaled to their median values. Empirical Bayesian estimates of individual infant PK parameters were generated from the final model using the post-hoc subroutine.

### *Model evaluation*

Models were evaluated based on successful minimization, goodness-of-fit plots, precision of parameter estimates, bootstrap procedures, and visual predictive check. The precision of the final population PK model parameter estimates was evaluated using parametric bootstrapping (1000 replicates) to generate the 95% confidence intervals (CIs) for parameter estimates. For the visual predictive check, the final model was used to generate 1000 Monte Carlo simulation replicates of piperacillin exposure, and simulated results were compared with those observed in the study. The number of observed concentrations outside of the 90% prediction interval for each time point was quantified.

### *Assessment of dose-exposure relationship*

Piperacillin demonstrates time-dependent pharmacodynamics (PD). For target exposure, we chose the time above a minimum inhibitory concentration (MIC) of 16–64 mg/L at steady state. This MIC target is consistent with the Clinical and Laboratory Standards Institute-recommended MIC susceptibility breakpoint of piperacillin/tazobactam for enteric gram-negative organisms such *Escherichia coli* and *Enterobacter* sp. (16 mg/L) and *Pseudomonas aeruginosa* (64 mg/L).<sup>7</sup> Monte Carlo simulations using the final



population PK model were used to explore dose-exposure relationships using these defined targets. Commonly used and current piperacillin dosing recommendations listed in Neofax<sup>8</sup> and The Harriet Lane Handbook<sup>9</sup> were used in these simulated datasets to evaluate target attainment rates at steady state. When a dosing range was recommended, the highest end of the range was chosen for the simulations. Target attainment rates were calculated for infants who achieved target piperacillin concentrations for 50% or 75% of the dosing interval. Inclusion of the more stringent PD target criteria (75% of the dosing interval) was derived from the assumption of an immuno-compromised state of preterm infants and the need to achieve higher drug concentrations to achieve bacterial killing.

## Results

### *Study population*

A total of 77 subjects from 5 centers were evaluated for analysis. Subjects were excluded from the analysis if dosing, concentration, or sampling data were unreliable (i.e., unable to discern time when sample was collected relative to dose administered) (N=13) and if sampling was obtained during line flush or during drug infusion and no other samples were collected (N=8). The exclusion of these subjects and samples resulted in 56 subjects from 5 sites with 211 concentrations used in the modeling process. The overall median (range) BGA, PNA, PMA, weight, SCR, and dose were 25 (22–32) weeks, 17 (1–77) days, 29 (23–40) weeks, 867 (400–2580) g, 0.8 (0.2–2.4) mg/dL, and 88 (39–147) mg/kg, respectively (Table 2.1). The majority of subjects were male (31/56, 56%) and white (29/56, 52%), and few were Hispanic (5/56, 9%).

### *PK specimens*

A total of 41/261 (16%) outlier drug concentrations were removed from the analysis due to unreliability of sampling times related to time of infusion (N=18), time of flush (N=20), or sample contamination (N=3). Six of these samples did not have any measurable piperacillin concentrations. The median time of PK sampling was 4.7 (0–11.16) hours after the dose, and the median concentration was 25.6 (0.041–502) mg/L. An average of 3.7 samples per infant (range, 1–22) was collected, and the overwhelming majority of PK samples were scavenged from the clinical laboratory (202/211, 96%). Sixteen samples (16/211, 7.6%) had concentrations below the limit of quantitation; 6/211 (2.8%) had a reliable signal above background noise documented on the LC/MS/MS instrument, and this measurement was used in the PK analysis. A value of zero was assigned to the remaining samples (10/211 [4.7%]) as they were below the level of detection.

### *Population PK model building*

A 1-compartment model was the appropriate structural PK model for this data set (Fig. 2.2). Because few samples were obtained within the first few hours post dose, it was not possible to estimate inter-compartmental clearance, and a 2-compartment model did not provide a better fit to the data. Weight was included in the base CL and V models (Table 2.2). Allometric scaling ( $\text{Weight}^{0.75}$ ) as well as estimation of the body size exponent ( $\text{Weight}^{\theta}$ ) were explored as potential body size models for CL and V. The exponent estimates for CL and V were 0.62 and 0.86, respectively. However, given strong physiologic basis and no improvement in model fit, exponents for weight were fixed at 0.75 and 1 for CL and V, respectively. In the base model, scatter plots showed a correlation between IIV on CL

(ETA1) and V (ETA2); a covariance term was added to the model. Age- and maturity-related covariates (BGA, PMA, PNA), as well as SCR, showed correlation with unexplained CL (ETA1) IIV (Fig. 2.1). During the univariable evaluation (after inclusion of body weight), all age-related covariates resulted in a significant decrease in the objective function value (OFV); however, the largest drop in OFV occurred when SCR was added to the model (Table 2.2). A SCR power model with exponent estimation did not improve the goodness of fit. CL estimated by SCR was superior to age-related models, and the addition of a maturation covariate (PMA) in the multivariable analysis did not improve the model goodness of fit (Tables 2.2 and 2.3). No other covariates were evaluated in the V model due to lack of correlation observed between the covariate and unexplained V (ETA2) IIV. Due to the low number of blood draw samples, bias introduced by scavenged specimen collection compared with timed blood draws around the dose could not be assessed.

#### *Population PK model evaluation*

The final model had good precision as evidenced by relative standard errors around the parameter point estimates of 13.7–32.2% and by 95% confidence intervals generated by bootstrapping (N=1000 simulated trials, 981 successful runs) (Table 2.3). Larger relative standard errors were observed for the point estimates of V. Goodness-of-fit diagnostic plots for the final model are shown in Fig. 2.2. The visual predictive check revealed a good fit between observed and predicted piperacillin concentrations (Fig. 2.3). Only 8.5% (18/211) of observed concentrations were outside of the 90% prediction interval.

### *Bayesian estimates of CL, V, and elimination half-life*

The median individual empirical Bayesian estimates for CL, V, and half-life were summarized by gestational age group (Table 2.4). There was a trend towards increasing median piperacillin weight-normalized CL with increasing BGA that was more apparent between infants <26 weeks BGA and infants 26–29 weeks BGA. Weight-adjusted piperacillin CL decreased with increasing SCR and, expectedly, did not change with increasing body weight (Fig. 2.4). Infants with SCR  $\geq 1.2$  mg/dL had a 60% lower CL value. Half-life decreased with increasing BGA group.

### *Dose-exposure relationship*

High failure rates were calculated when the surrogate PD targets of time above MIC of 16 and 64 mg/L for 50% and 75% of the dosing interval were evaluated. Only 60% of all infants achieved piperacillin concentrations >16 mg/L for 50% of the dosing interval. Only 30% of infants  $\leq 29$  weeks and none of those 30–32 weeks BGA achieved piperacillin concentrations >64 mg/L for 50% of the dosing interval (Fig. 2.5). When the same targets were evaluated for 75% of the dosing interval, 50% of all infants achieved piperacillin concentrations >16 mg/L; 15% of infants  $\leq 29$  weeks and none of those 30–32 weeks BGA achieved piperacillin concentrations >64 mg/L for 75% of the dosing interval. Monte Carlo simulations using the final population PK model were used to explore dose-exposure relationships using current piperacillin dosing recommendations. Overall, dosing recommendations by Neofax (100 mg/kg every 8–12 hours) and The Harriet Lane Handbook (75 mg/kg every 8–12 hours) produced similar piperacillin exposures in simulated datasets; only 40–60% of infants across BGA achieved the PD target of concentrations above 16 mg/L

for 50% of the dosing interval. Piperacillin concentrations  $>64$  mg/L for 75% of the dosing interval were achieved in the minority of simulated patients ( $<25\%$ ); this finding was most pronounced among infants 30–32 weeks BGA (Fig. 2.5).

## Discussion

Most antimicrobial products used in preterm infants lack some aspect of PK information specific to this population. Without appropriate studies specifically designed for preterm infants, clinicians are often forced to prescribe products “off-label,” exposing patients to potential adverse drug effects or less-than-optimal drug exposure without dosing evidence.<sup>10,11</sup>

The primary goal was to evaluate the PK of piperacillin in this population, evaluate potential covariates that would explain inter-individual variability in PK parameters, and assess the potential bias introduced by scavenged sampling compared with traditional sampling per study protocol. A population PK approach allowed for the use of sparse sampling, and stratified enrollment ensured a broad distribution of BGA and PNA.

In the present model, piperacillin CL increased with allometrically scaled body weight, and it decreased proportionally with increasing SCR. Allometric size adjustments in PK parameters have been well established as appropriate and physiologic-based models to describe CL changes among neonates and preterm infants.<sup>6,12</sup> The association of CL with SCR is expected due to the high proportion ( $>70\%$ ) of piperacillin excreted in the urine.<sup>3</sup> However, the clinical utility of SCR in preterm infants during the first few days of life is debated due to the confounding effect of maternal creatinine. Because only 3 (5%) of subjects in this study were  $<3$  days of life, it is unlikely that bias was introduced by maternal

creatinine contamination. The addition of maturational components (i.e., BGA, PNA, PMA) into the multivariable CL model did not change the goodness of fit nor did it explain remaining IIV. Due to ontogenic changes in renal function among preterm infants, SCR is strongly linked with maturational components such as BGA, PNA, and PMA. A correlation matrix between covariates included in this study revealed this association. This observation likely prevented the ability to discern the effect of each maturational component in CL IIV from SCR in the CL model-building process. Weight was the only covariate that explained V IIV, consistent with other studies in preterm infants.<sup>12</sup>

The population PK model developed performed well and showed good precision around parameter estimates. A high degree of IIV in CL (91.5% coefficient of variation [CV]), V (119 CV%), and residual variability (RV, 73.8 CV%) was observed. The large IIV in CL and V could have resulted from the diversity of study subjects included in this trial. However, large unexplained IIV in CL and V remained in the final model after inclusion of significant covariates. Because study efficiency was an important part of the study design, data collection (demographics and other clinically relevant covariates) was limited. The unexplained IIV could be attributed to other covariates not included in the study (i.e., concomitant medications). The large RV observed could be the result of several factors, such as documentation errors in sampling or dosing times, model misspecification, and drug degradation in scavenged samples. Ambient and refrigerator storage may affect piperacillin stability in plasma.<sup>13,14</sup> Information regarding the duration and conditions under which the samples remained in the clinical laboratory before freezing were not collected, which limits our ability to assess the reliability of drug concentrations in scavenged samples. Because very few samples were drawn specifically for the study, the comparison between traditional and

scavenged sampling schemes was not possible. Large RV was unlikely to be the result of drug concentration measurements given that the assay was validated according to FDA criteria.<sup>15</sup>

Because this study did not evaluate efficacy or clinical outcomes, surrogate piperacillin PD end points were used for the study population receiving piperacillin per routine clinical care and in simulated datasets including current dosing recommendations from commonly used pediatric resources.<sup>8,9</sup> The proportion of patients achieving surrogate PD targets for efficacy was suboptimal. A substantial proportion of subjects (~40%) did not achieve piperacillin concentrations efficacious against common gram-negative enteric bacteria (i.e. *Escherichia coli*, enterobacter), and the vast majority (~70%) did not achieve concentrations above the susceptibility breakpoint for more resistant organisms such as *Pseudomonas aeruginosa*. A similar pattern was observed among simulated datasets using current dosing recommendation guidelines. Dosing by Neofax or The Harriet Lane Handbook resulted in similar target attainment rates, but similar to targets in the actual patient population, outcomes were suboptimal. These findings could suggest that current dosing per standard of care or as recommended in common pediatric resources is inadequate for this patient population. However, this should be interpreted with caution because lower (2–10-fold) than previously observed piperacillin concentrations<sup>2,4</sup> were observed in this study, possibly as a result of scavenged sampling.

Our understanding of the PK of piperacillin in preterm infants is extremely limited. A single-center, single-dose PK study of piperacillin (75 mg/kg) conducted in 28 newborn infants with BGA of 29–40 weeks and PNA of 3–11 days demonstrated an increase in clearance with increasing gestational age.<sup>4</sup> This study, however, excluded neonates <28

weeks estimated gestational age and infants beyond the second week of life. It is therefore difficult to compare our study results to this prior study, but overall the individual empirical Bayesian CL and V estimates of the present study were higher (2–10-fold) than previously reported after controlling for BGA and PMA. V estimates were particularly large when compared with other patient populations including older infants and adults.<sup>2,3</sup> A large piperacillin V would be expected in preterm infants due to the high total water content relative to body mass<sup>16</sup> and the hydrophilic nature of the drug. Alternatively, higher than expected CL and V estimates are likely the result of low piperacillin concentrations encountered in this trial. As mentioned, drug degradation in scavenged samples may have accounted for the low concentrations observed.

In summary, minimal-risk methods such as scavenged PK sampling can provide meaningful information related to development of structural PK models, as well as potential covariates that explain IIV in PK parameters. After allometric scaling, incorporating SCR as a CL model increased the model fit, and dose adjustments will likely be needed based on this parameter. The utility of scavenged sampling in providing dosing recommendations, however, is drug-dependent and likely not useful for unstable drugs such as piperacillin without stringent criteria regarding handling or documentation of handling to eliminate degraded samples from analysis. Future efforts evaluating this methodology should consider the physicochemical properties of the drug, more detailed documentation of sample collection and storage conditions, and simultaneous collection of traditional plasma samples to fully assess the extent of bias introduced by scavenged sampling.



## References

1. Michelow IC, McCracken GH Jr. Antibacterial therapeutic agents. In Feigin RD, ed. *Textbook of Pediatric Infectious Diseases*. Philadelphia, PA: Saunders;2004:2990–2991.
2. Reed MD, Goldfarb J, Yamashita TS, Lemon E, Blumer JL. Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother*. 1994;38(12):2817–2826.
3. Tjandramaga TB, Mullie A, Verbesselt R, De Schepper PJ, Verbist L. Piperacillin: human pharmacokinetics after intravenous and intramuscular administration. *Antimicrob Agents Chemother*. 1978;14(6):829–837.
4. Kacet N, Roussel-Delvallez M, Gremillet C, Dubos JP, Storme L, Lequien P. Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. *Pediatr Infect Dis J*. 1992;11(5):365–369.
5. Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol*. 2009;24(1):67–76.
6. Wade KC, Wu D, Kaufman DA, Ward RM, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother*. 2008;52(11):4043–4049.
7. Eagye KJ, Kuti JL, Sutherland CA, Christensen H, Nicolau DP. In vitro activity and pharmacodynamics of commonly used antibiotics against adult systemic isolates of *Escherichia coli* and *Pseudomonas aeruginosa* at 40 U.S. hospitals. *Clin Ther*. 2009;31(11):2678–2688.
8. Thomson Reuters Clinical Editorial Staff. *Neofax 2011*. 24th ed. Montvale, NJ: Thomson Reuters; 2011.
9. Tschudy M, Arcara K. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*. 19th ed. Philadelphia, PA: Mosby; 2011:1035.
10. Choonara I. Unlicensed and off-label drug use in children: implications for safety. *Expert Opin Drug Saf*. 2004;3(2):81–83.
11. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA*. 2003;290(7):905–911.
12. Suyagh M, Collier PS, Millership JS, et al. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. *Pediatrics*. 2011;127(2):e367–e374.

13. Arzuaga A, Isla A, Gascón AR, et al. Quantitation and stability of piperacillin and tazobactam in plasma and ultrafiltrate from patients undergoing continuous venovenous hemofiltration by HPLC. *Biomed Chromatogr.* 2005;19(8):570–578.
14. Denooz R, Charlier C. Simultaneous determination of 5 beta-lactam antibiotics (cefepim, ceftazidim, cefuroxim, meropenem and piperacillin) in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2008;864(1–2):161–167.
15. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine. *Guidance for Industry: Bioanalytical Method Validation.* Rockville, MD: Food and Drug Administration; 2001.
16. Fomon SJ, Haschke F, Ziegler EE, Nelson SE. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr.* 1982;35(5 Suppl):1169–1175.

Table 2.1. Clinical data by gestational age group

Characteristic	Gestational age at birth (weeks)		
	<26	26–29	30–32
N	29	20	7
Gestational age, weeks	24 (22, 25)	27 (26, 29)	31 (28, 32)
Postnatal age, days	17 (1, 77)	15 (1, 75)	24 (3, 65)
Postmenstrual age, weeks	27 (23, 35)	30 (27, 38)	35 (31, 40)
Weight, g	709 (400, 1400)	1023 (555, 2580)	1610 (1357, 1890)
Female sex	14 (48)	5 (25)	6 (86)
Race			
White	15 (52)	10 (50)	4 (57)
Black	12 (41)	9 (45)	2 (29)
Other	2 (7)	1 (5)	1 (14)
Hispanic	2 (7)	1 (5)	2 (29)
Serum creatinine (mg/dL)	1 (0.3, 2.4)	0.8 (0.2,2)	0.5 (0.2,0.9)
Dose (mg/kg)	80 (43,147)	87 (44,116)	100 (39,110)
Dosing frequency (h)	8 (6,14)	8 (6,13)	8 (6,16)

Data are median (range) for continuous data and n (%) for categorical data.

Table 2.2. Model-building process

Base model and univariable analysis			
analysis	Population model	OFV	$\Delta$ OFV
V	$V = \theta_V \times (\text{wt})^1$	1653	-
CL base model	$CL = \theta_{CL} \times (\text{wt})^{0.75}$	1653	-
BGA	$CL = \theta_{CL} \times (\text{wt})^{0.75} \times (\text{BGA}/25)^{\theta_{CL-BGA}}$	1647	-6
PMA	$CL = \theta_{CL} \times (\text{wt})^{0.75} \times (\text{PMA}/29)^{\theta_{CL-PMA}}$	1643	-10
PNA	$CL = \theta_{CL} \times (\text{wt})^{0.75} \times (\text{PNA}/17)^{\theta_{CL-PNA}}$	1645	-8
SCR	$CL = \theta_{CL} \times (\text{wt})^{0.75} \times (0.5/\text{SCR})$	1618	-35
Multivariable model			
CL, PMA, and SCR	$CL = \theta_{CL} \times (\text{wt})^{0.75} \times (0.5/\text{SCR}) \times (\text{PMA}/29)^{\theta_{CL-PMA}}$	1618	0

V: volume of distribution; CL: clearance; BGA: gestational age at birth; PMA: postmenstrual age; PNA: postnatal age; SCR: serum creatinine (mg/dL); wt: weight; OFV: objective function value.

Table 2.3. Final population pharmacokinetic model parameter estimates

Parameter	Symbol	Point estimate	%RSE	Bootstrap CI		
				2.5%	Median	97.5%
CL (L/h)	$\theta_{CL}$	0.479	13.7	0.352	0.466	0.606
V (L)	$\theta_v$	2.91	30.8	1.640	2.935	5.615
Inter-individual variance						
CL (CV%)	$\omega^2_{CL}$	91.54	19.5	83.86	94.88	103.87
V (CV%)	$\omega^2_v$	119.16	32.2	88.39	108.54	124.14
CL vs. V correlation	$\omega^2_{CL-V}$	1.03	21.5	0.94	0.98	1.00
Residual variance (CV%)						
	$\sigma^2$	73.82	13.7	79.25	85.56	91.27

CL: clearance; V: volume of distribution; CV: coefficient of variation; CI: confidence interval; RSE: relative standard error.

Table 2.4. Individual empirical Bayesian pharmacokinetic parameter estimates by gestational age group

Gestational age (weeks)	CL (L/h)	95% CI	CL (L/h/kg)	95% CI	V (L)	95% CI	V (L/kg)	95% CI	Half-life (h)	95% CI
<26	0.239	0.048, 1.286	0.311	0.069, 1.303	2.15	0.32, 16.99	3.44	0.51, 20.91	8.8	2.7, 16.8
26-29	0.401	0.037, 1.306	0.371	0.055, 0.777	2.44	0.40, 10.09	2.83	0.39, 9.21	5.9	1.5, 17.4
30-32	0.393	0.248, 1.612	0.261	0.145, 1.671	3.38	1.47, 17.98	2.42	0.86, 13.25	4.5	1.6, 7.7
<b>Overall</b>	<b>0.302</b>	<b>0.044, 1.612</b>	<b>0.338</b>	<b>0.067, 1.303</b>	<b>2.75</b>	<b>0.32, 16.99</b>	<b>2.72</b>	<b>0.48, 17.16</b>	<b>6.9</b>	<b>1.7, 16.7</b>

CL: clearance, V: volume of distribution; CI: confidence interval.

Fig. 2.1. Base model scatter plots of CL ETA1 estimates and the following: BGA (A), PNA (B), PMA (C), and SCR (D).

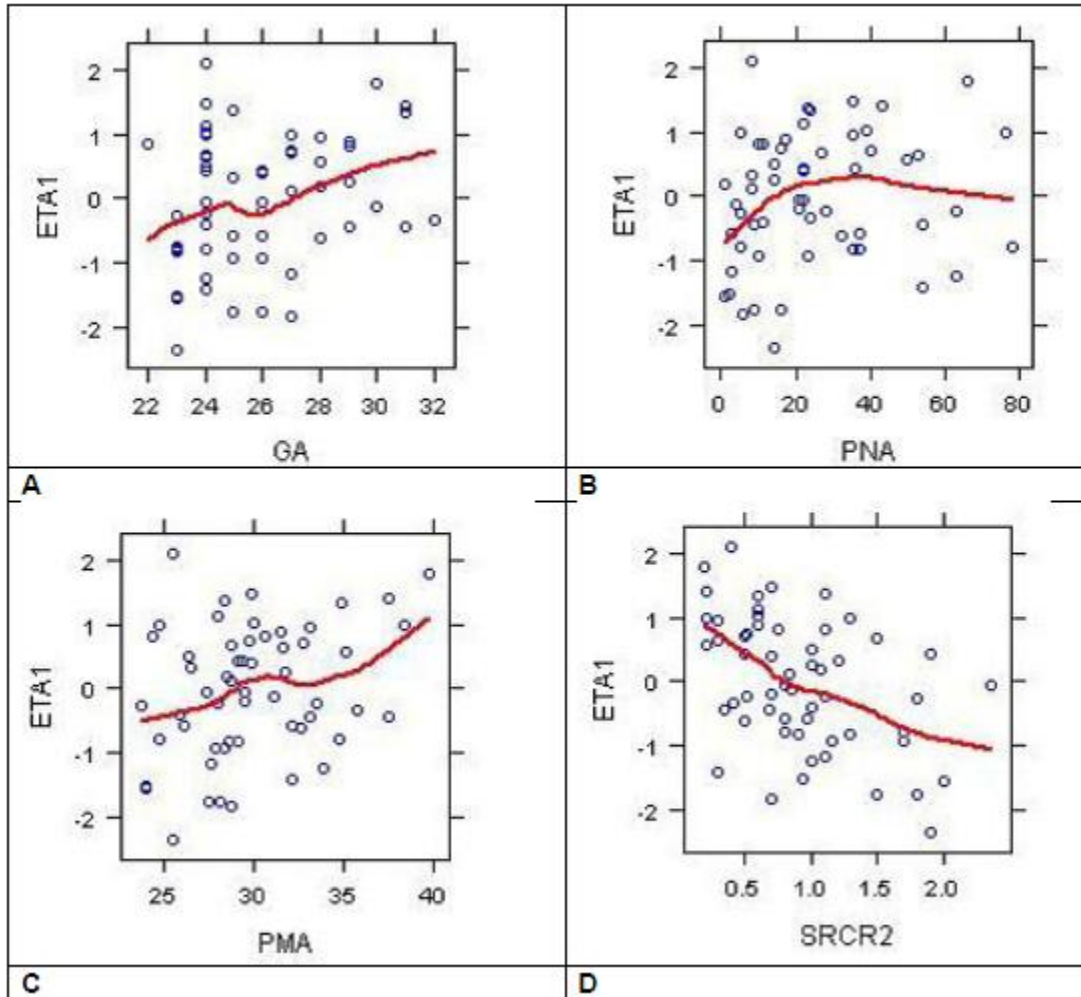


Fig. 2.2. Final population pharmacokinetic model diagnostic plots: observed vs. population prediction (A) and individual prediction (B), weighted residuals vs. population predictions (C) and time (D). For A and B, the line of identity is included as a reference. For weighted residuals, a solid line at  $y=0$  is included as a reference.

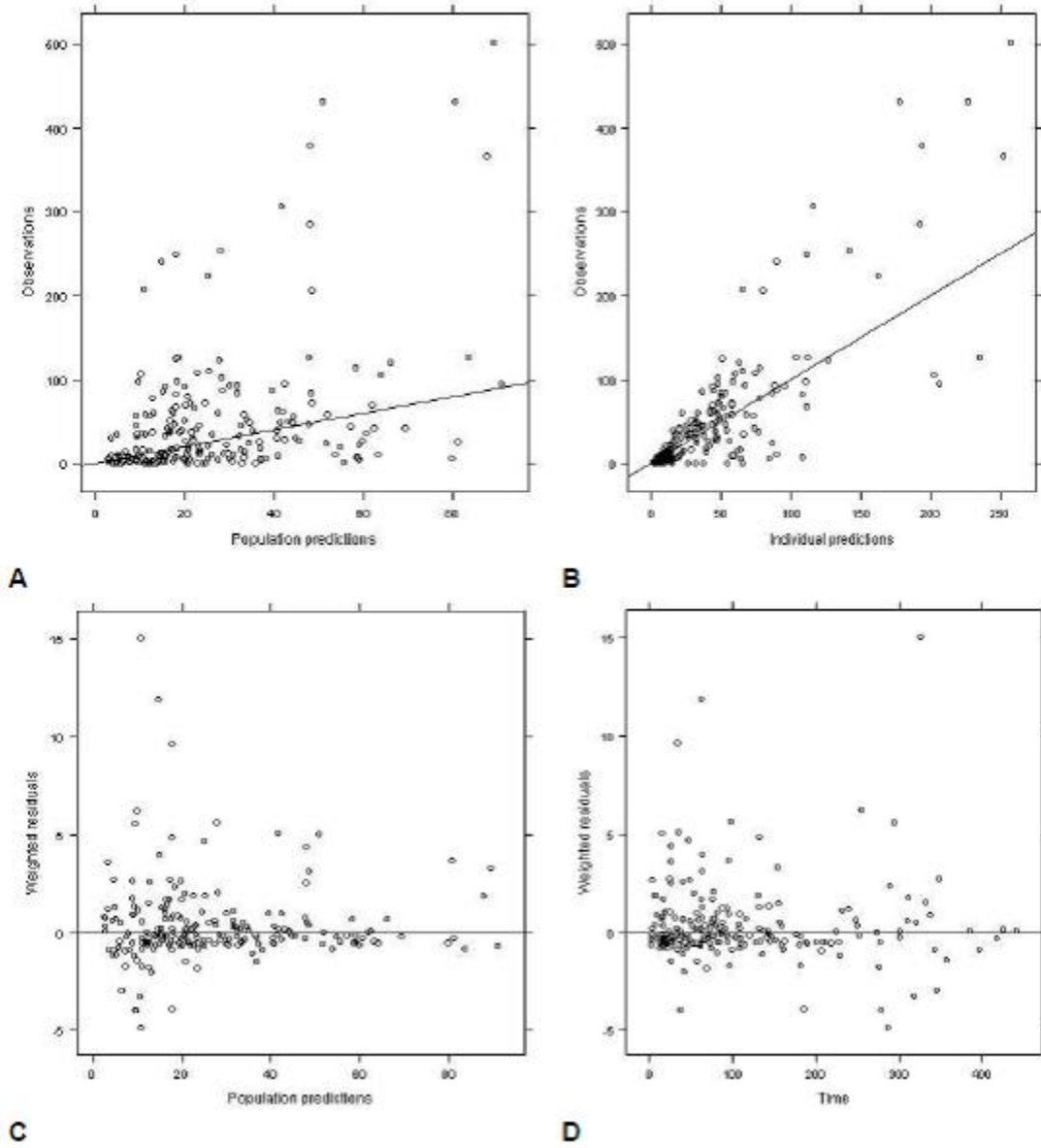




Fig. 2.3. Visual predictive check of piperacillin dose-normalized concentrations versus time. Solid black circles represent observed concentrations. Shaded gray area represents the 90% prediction interval. Solid and dashed black lines represent observed and predicted median concentrations, respectively.

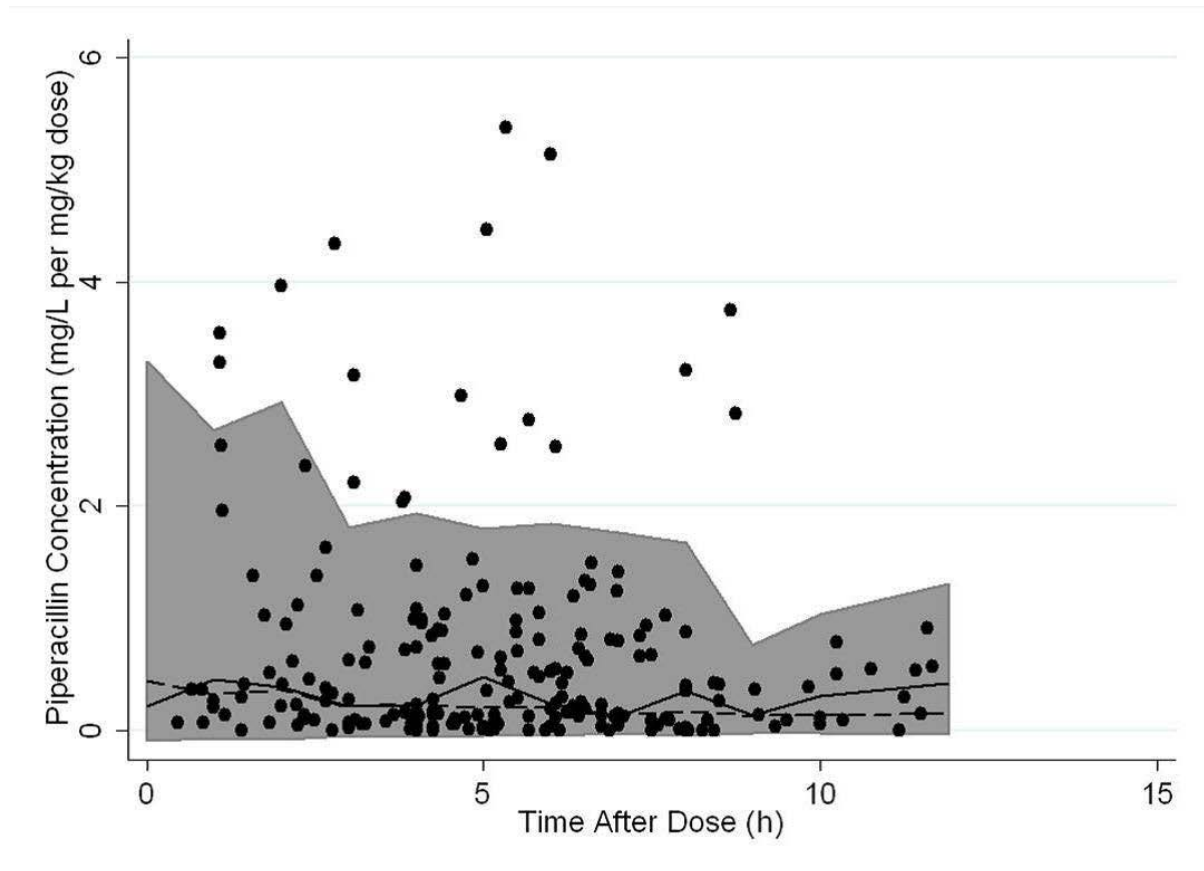
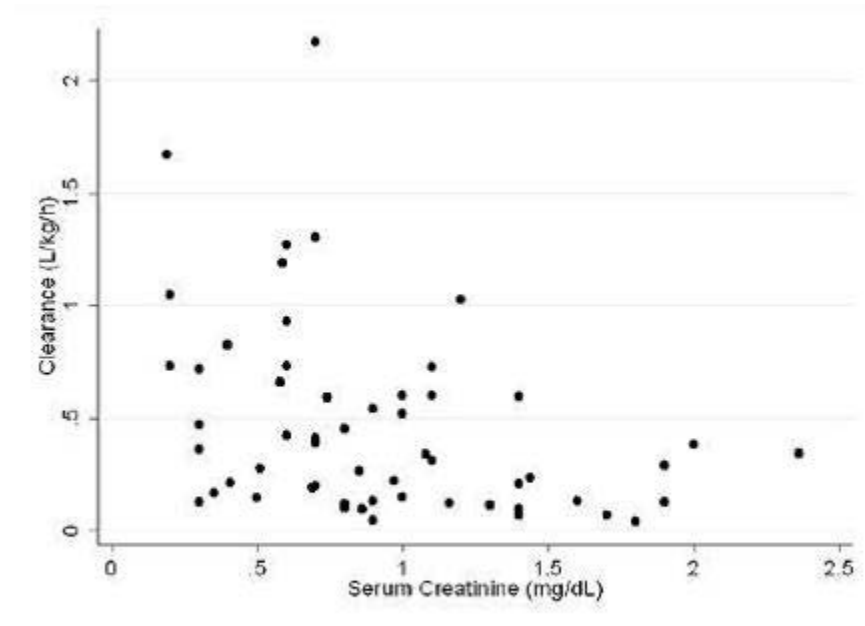
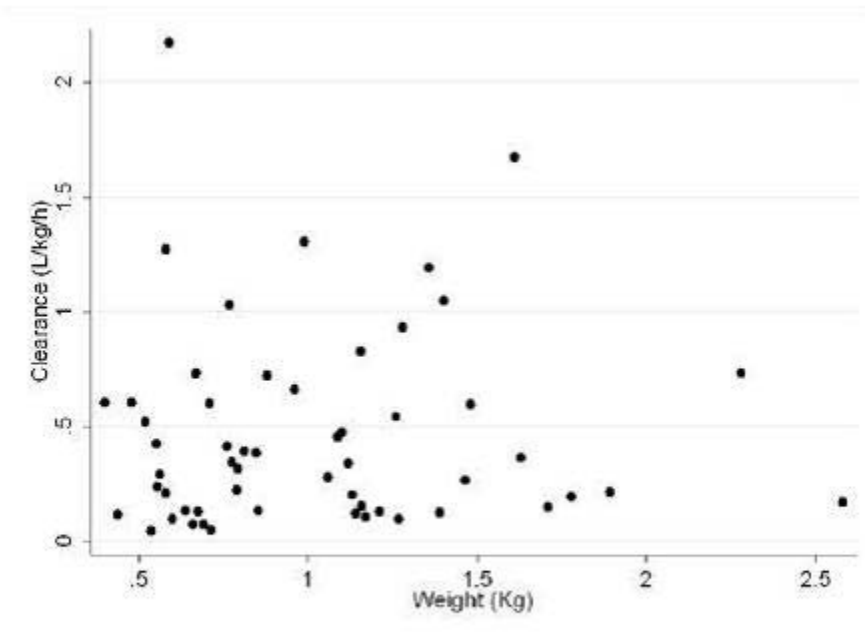


Fig. 2.4. Weight-normalized piperacillin clearance versus serum creatinine (A) and body weight (B).

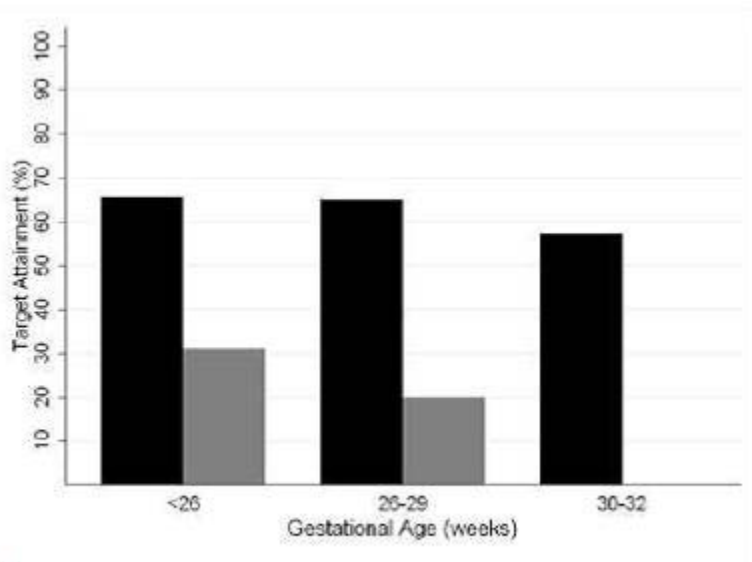


**A**

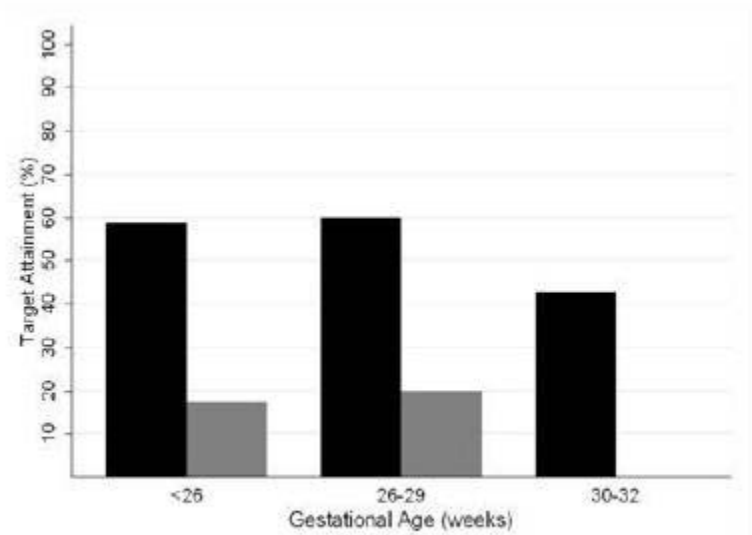


**B**

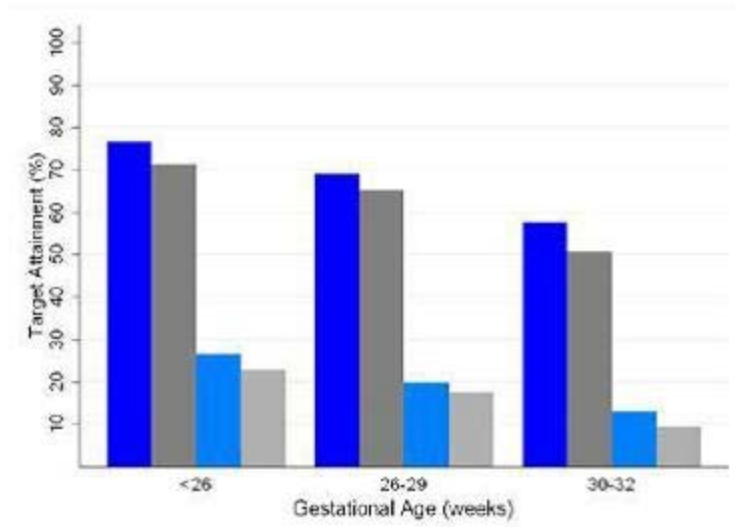
Fig. 2.5. Pharmacodynamic target attainment rates by gestational age group. A: Proportion of patients who met PD target of desired concentrations for 50% of the dosing interval (black bar: 16 mg/L, gray bar: 64 mg/L); B: Proportion of patients who met PD target of desired concentrations for 75% of the dosing interval (black bar: 16 mg/L, gray bar: 64 mg/L); C: Proportion of simulated patients who met PD target of desired concentrations for 50% of the dosing interval (dark blue bar: Neofax 16 mg/L, light blue bar: Neofax 64 mg/L, dark gray bar: The Harriet Lane Handbook 16 mg/L, light gray bar: The Harriet Lane Handbook 64 mg/L); D: Proportion of simulated patients who met PD target of desired concentrations for 75% of the dosing interval (dark blue bar: Neofax 16 mg/L, light blue bar: Neofax 64 mg/L, dark gray bar: The Harriet Lane Handbook 16 mg/L, light gray bar: The Harriet Lane Handbook 64 mg/L).



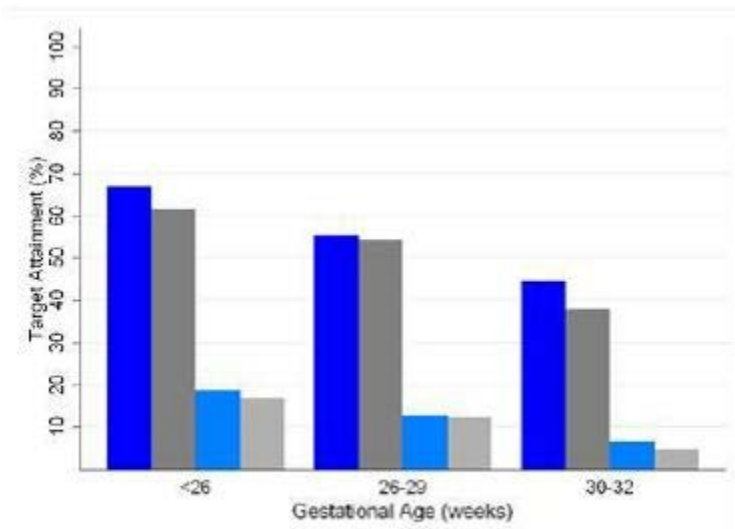
**A**



**B**



C



D

## CHAPTER III: POPULATION PHARMACOKINETICS OF METRONIDAZOLE USING SCAVENGED SAMPLES FROM PRETERM INFANTS

### Introduction

Preterm infant pharmacokinetic (PK) studies are exceptionally scarce due to the research challenges posed by this population, such as limited blood volume for PK sampling, difficulty in timing of PK samples due to the critical medical condition of the infants, difficult access to obtain samples, and low parental informed consent rates. Feasibility issues also are imposed by traditional PK study designs, which require large numbers of specifically timed PK blood samples. These difficulties have encouraged investigators to explore novel minimal-risk methods to evaluate the PK of antimicrobials in this population. One proposed method is the use of scavenged samples left over from the normal clinical care of infants. The use of scavenged samples for PK studies in preterm infants offers several advantages over traditional timed PK trials. These include avoiding the need for heel sticks specifically for the study; higher rates of parental consent due to perceived minimal risk; availability of several samples per infant; and avoidance of time-specific PK sampling.<sup>1</sup> This methodology, combined with collection of timed PK samples (collected specifically for study purposes), has proven successful in the evaluation of fluconazole PK in preterm infants.<sup>1</sup> To our knowledge, the use of scavenged samples for PK analysis of other antimicrobials has not been evaluated.

Metronidazole is approved by the U.S. Food and Drug Administration for the treatment of adults with serious infections caused by susceptible anaerobic bacteria but is not approved for use in children. In spite of this, metronidazole is extensively used “off-label” in children to treat anaerobic intra-abdominal infections (i.e., perforated appendicitis).<sup>2</sup> In young infants, its use is typically restricted to treatment of rare cases of anaerobic bacteremia, central nervous system infections, and complicated intra-abdominal infections such as necrotizing enterocolitis.<sup>3,4</sup> Because infection in young infants with very low birth weight (<1500 g birth weight) is associated with devastating outcomes including death and neurodevelopmental impairment, appropriate dosing recommendations for agents such as metronidazole are needed in this population.

Metronidazole dosing recommendations for preterm infants listed in commonly used reference sources for pediatric practitioners are based on a combination of birth weight and postnatal age (PNA)<sup>5</sup> or birth gestational age (BGA) and postmenstrual age (PMA).<sup>6</sup> These recommendations are derived from small, single-center studies and have not been prospectively evaluated. In addition, these dosing regimens are cumbersome due to the different combinations of maturation components required to choose the most appropriate dose. PMA-based dosing offers an advantage over current recommendations by simplifying dosing regimens and potentially providing desired metronidazole concentrations over a wider age range. PMA-based dosing has not been systematically evaluated for metronidazole; however, it has been proven successful for other therapeutics in preterm infants.<sup>7-9</sup>

The present study was conducted to assess the population PK of intravenous metronidazole using scavenged samples collected from preterm infants <32 weeks BGA.

## Methods

### *Study design*

PK samples for this analysis were obtained from the Antimicrobial PK in High-Risk Infants trial sponsored by the Pediatric Pharmacology Research Unit (PPRU). This trial was a multi-center, prospective, open-label PK study of antimicrobial agents commonly used in the neonatal intensive care unit. Infants  $\leq 32$  weeks GA at birth and  $< 120$  days of age receiving intravenous metronidazole per routine medical care were enrolled. Metronidazole dosing was determined by the routine clinical practice in each unit, and no exclusion criteria were used. To evaluate the effect of maturation on metronidazole PK, infants were stratified at enrollment by GA:  $< 26$  weeks, 26–29 weeks, and 30–32 weeks. The study was approved by the institutional review boards at each institution, and informed consent was obtained from a parent or guardian prior to enrollment.

The following information was collected for covariate analysis: BGA, PNA, PMA, weight, sex, race, serum creatinine (SCR), and ethnicity. Covariates that exhibited time-dependent changes (e.g., weight, PNA) were permitted to change with time, and the actual value in the data set reflects the observations made at each patient visit. Missing weights were imputed with the last recorded value carried forward for up to 7 days. SCR was recorded when obtained for clinical care. Missing SCR values were imputed based on an exponential model of SCR and PMA derived from the data.<sup>10</sup>

### *PK sample collection*

A sparse sampling approach was followed in this study. Samples were divided into 2 types: scavenged and blood draw. *Scavenged samples* were defined as samples obtained

without obtaining additional blood from the infant. These samples were collected from the clinical laboratory from discarded blood (heparinized or ethylenediaminetetraacetic acid [EDTA] tubes) obtained for routine clinical care. *Blood draw samples* were defined as samples obtained with collection of extra blood from the infant. Each blood draw was approximately 0.3 mL of blood collected in EDTA Microtainers. PK sample collection was planned at the following time points: immediately prior to metronidazole infusion, immediately after the completion of infusion ( $t=0$ ), approximately 1–1.5 hours after completion of infusion ( $t=1-1.5$  hour), approximately 3–4 hours after completion of infusion ( $t=3-4$  hours), and immediately prior to infusion of the next dose. The duration of metronidazole infusion was performed according to site routine clinical care. Samples were refrigerated or placed on ice immediately after collection and then centrifuged at 1500 g and 4° C for 10 minutes. Plasma was removed and stored at -70° C. Samples from all sites were shipped on dry ice to Duke University Medical Center where they were stored at -70° C prior to analysis. Samples were stored for a maximum of 32 months prior to analysis.

#### *Bioanalytical assay*

A liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) assay for metronidazole detection in human plasma suitable for small plasma volumes was developed and validated.<sup>11</sup> Briefly, sample analysis was performed on a triple quadrupole mass spectrometer API 4000 (Applied Biosystems–ABSciex, Foster City, CA, USA) operated with electrospray ionization (TurboV source using a TurboIonspray® probe). Instrument parameters were optimized for the metronidazole transition (172.1→128.1 m/z). HPLC separation was achieved using a reverse-phase C18 Aquasil column (Thermo Fisher,



Waltham, MA, USA) with a flow-rate of 0.75 ml/min using a gradient mobile phase. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in methanol. Analytical data were acquired by Analyst Software 1.4.1 (Applied Biosystems–ABSciex, Foster City, CA, USA). The lower limit of quantitation of metronidazole in plasma was 0.05 mg/L. Intraday and interday coefficients of variation were <9.5% at concentrations ranging from 0.05–25 mg/L.

#### *Population PK analysis*

PK data were analyzed with a nonlinear mixed effect modeling (NONMEM) approach using the computer program NONMEM (version 7) in conjunction with WINGS for NONMEM version 7.03 (Auckland, NZ). Output was summarized using STATA 10 (College Station, TX, USA). The first-order conditional estimation method with interaction was used for all model runs. One- and 2-compartment structural PK models were evaluated. Inter-individual (IIV) random effects were evaluated on clearance (CL) and volume of distribution (V). An exponential model for IIV variance was used, and a proportional error model was deemed appropriate to describe residual variability. The potential impact of clinical covariates on PK parameters was explored if a relationship was suggested by visual inspection of scatter and box plots (continuous and categorical variables, respectively) of individual Bayesian estimates obtained from the base model and CL IIV (ETA) against covariates. The following covariates were evaluated: weight (kg), BGA (weeks), PNA (days), PMA (defined as GA plus PNA in weeks [PNA/7]), SCR, race, sex, and ethnicity. An SCR model including an indicator variable (CR) that excluded a potential outlier with an SCR of 4.7 mg/dL was also evaluated. Once covariates were identified during the model-

building process, covariate testing was performed via standard forward addition backward elimination methods. Potential covariates that reduced the objective function by more than 3.84 ( $P < \sim 0.05$ ) were included in the subsequent multivariable analysis. A forward inclusion with backwards elimination approach was used during the multivariable step, and a reduction of 6.63 ( $P < \sim 0.01$ ) was required for retention of a covariate in the final model. Continuous covariates were scaled to their median values. Empirical Bayesian estimates of individual infant PK parameters were generated from the final model using the post-hoc subroutine. Bias introduced by scavenged specimens was evaluated in the random effects error model of the final population model using a fixed effect parameter ( $\theta^{\text{SCAV}}$ ), as well as different residual variability estimates for blood draws and scavenged samples. An indicator variable (SCAV) was used to identify scavenged samples (SCAV = 1).

### *Model evaluation*

Models were evaluated based on successful minimization, goodness-of-fit plots, precision of parameter estimates, bootstrap procedures, and visual predictive check. The precision of the final population PK model parameter estimates were evaluated using non-parametric bootstrapping (1000 replicates) to generate the 95% confidence intervals (CIs) for parameter estimates. For the visual predictive check, the final model was used to generate 1000 Monte Carlo simulation replicates of metronidazole exposure, and simulated results were compared with those observed in the study. The number of observed concentrations outside the 90% prediction interval for each time point was quantified.

### *Assessment of dose-exposure relationship*

Surrogate pharmacodynamic (PD) targets for metronidazole against anaerobic bacteria are poorly defined.<sup>12</sup> Therefore, for target exposure, a minimum inhibitory concentration (MIC) of 8 mg/L at steady state was chosen as the surrogate efficacy target. This MIC target is consistent with the Clinical and Laboratory Standards Institute (CLSI)-recommended MIC susceptibility breakpoint of metronidazole for anaerobic organisms.<sup>13</sup> Metronidazole trough concentrations at steady state were predicted for each subject using individual empirical Bayesian estimates from the final model and dosing prescribed in the study per routine medical care. The proportion of subjects in the study who met the PD target was calculated by GA group. In addition, Monte Carlo simulations (N=1000) using the final population PK model were used to explore dose-exposure relationships of commonly used metronidazole dosing recommendations listed in Neofax<sup>6</sup> and The Harriet Lane Handbook,<sup>5</sup> as well as a newly proposed, more simplistic dosing regimen based on PMA (Table 3.1). When a dosing range was recommended, the highest end of the range was chosen for the simulations. The proportion of simulated subjects who met the PD target was calculated by GA group and PNA. Additionally, Monte Carlo simulations (N=100) using the final population PK model fixed and random effects estimates were performed to predict metronidazole concentrations in typical subjects receiving the newly proposed PMA-based dosing regimen including a loading dose. These typical subjects included an infant with PMA 26 weeks (weight 900 g); 1 with PMA 32 weeks (weight 1900 g); 1 with PMA 36 weeks (weight 2800 g); and 1 with PMA 41 weeks (weight 3800 g).

## Results

### *Study population*

Thirty-three subjects from 5 centers were evaluated for analysis. One subject was excluded from the analysis because sampling was obtained during drug infusion and no other samples were collected. The overall median (range) GA, PNA, PMA, weight, SCR, and dose were 27 (22–32) weeks, 41 (0–97) days, 32 (24–43) weeks, 1495 (678–3850) g, 0.5 (0.1–4.7) mg/dL, and 8 (4–15) mg/kg, respectively (Table 3.2). The majority of subjects were female (17/32 [53%]). Sixteen (50%) were white, and 4 (9%) were Hispanic.

### *PK specimens*

A total of 3/119 (2.5%) outlier concentrations were removed from the analysis due to unreliability of sampling times related to time of flush (N=2) or sample contamination (N=1). The exclusion of these subjects and samples resulted in 32 subjects from 5 sites with 116 concentrations used in the modeling process. The median time of PK sampling was 6.5 (0.5–24) hours after dose, and the median concentration was 14.5 (1.31–68.5) mg/L. An average of 3.6 samples per infant (range, 1–15) was collected, and the majority of PK samples were scavenged from the clinical laboratory (104/116, 90%).

### *Population PK model building*

A 1-compartment model was the appropriate structural PK model for this data set (Fig. 3.2). Because few samples were obtained within the first few hours post dose, inter-compartmental clearance was not estimated and a 2-compartment model did not provide a better fit to the data. Weight was included in the base CL and V models (Table 3.3). An

estimation of the body size exponent (weight<sup>θ</sup>) was explored as a potential body size model for CL and V; however, it was excluded due to lack of improvement in model fit and imprecision around the exponent parameter estimate. After incorporating weight in the base model, it was not possible to estimate IIV in V. An evaluation of the model prior to the addition of weight as a covariate for V demonstrated high shrinkage in V IIV (47%). This finding suggested that the V IIV parameter estimate deviated from a normal distribution leading to non-parametric estimation of this parameter. However, once weight was reincorporated into the model, the V IIV parameter was estimated with a value close to zero via non-parametric methods and was excluded during the model-building process. Age- and maturity-related covariates (PNA, PMA) as well as SCR showed correlation with unexplained CL (ETA1) IIV (Fig. 3.1). During the univariable evaluation (after inclusion of body weight), all age-related covariates as well as SCR resulted in a significant decrease in the objective function value (OFV) (Table 3.3). The largest drop in OFV occurred when SCR was added to the model. However, when the SCR outlier indicator variable was used, the change in OFV was not as pronounced as that observed with addition of maturation covariates. This suggested that the significant association between SCR and CL was influenced by an outlier observation (Table 3.3). In the multivariable analysis, the addition of SCR did not improve the model goodness of fit nor did it significantly decrease the OFV (Tables 3.3 and 3.4). When the bias of scavenged samples was evaluated in the error model of the final population PK model, underestimation of metronidazole concentrations by 30% (95% CI 10–42%) was observed (Table 3.4).

### *Population PK model evaluation*

The final model had good precision as evidenced by relative standard errors around the parameter point estimates of 11–30% and by 95% confidence intervals generated by bootstrapping (N=1000 simulated trials, 997 successful runs) (Table 3.4). Goodness-of-fit diagnostic plots for the final model are shown in Fig. 3.2. The visual predictive check revealed a good fit between observed and predicted metronidazole concentrations (Fig. 3.3). Only 7% (8/116) of observed concentrations were outside of the 90% prediction interval.

### *Bayesian estimates of CL, V, and half-life*

The median individual empirical Bayesian estimates for CL, V, and half-life were summarized by GA group (Table 3.5). There was a trend towards increasing median metronidazole weight-normalized CL and decreasing half-life with increasing GA group. Consistent with the PMA covariate influence in the final population PK model, weight-adjusted metronidazole CL increased with increasing PMA and decreased with increasing SCR (Fig. 3.4).

### *Dose-exposure relationship*

Over 70% of all infants included in this study achieved the PD target (steady-state trough concentrations > than an MIC of 8 mg/L) (Fig. 3.5, Table 3.2). In contrast, <70% of subjects across GA groups achieved the target when dosing recommendations by Neofax and The Harriet Lane Handbook were used in simulated datasets (Fig. 3.5 and 3.6). The smallest proportion of preterm infants who achieved the PD target was observed in the 30–32-weeks BGA group and infants with PNA >60 days (Fig. 3.5 and 3.6). In contrast, 90% of subjects

regardless of BGA group and PNA achieved the target when the PMA-based dosing scheme was used in simulated datasets. Higher steady-state metronidazole trough concentrations were predicted by the PMA-based dosing regimen when compared with the other regimens, and therapeutic concentrations (median) were achieved after a loading dose on the first day of therapy (Fig. 3.5 and 3.7).

## Discussion

Most antimicrobial products used in preterm infants lack PK information specific to the unique physiology of prematurity. Without appropriate studies specifically designed for preterm infants, clinicians are often forced to prescribe products “off-label,” exposing patients to potential adverse drug effects or less-than-optimal drug exposure without dosing evidence.<sup>14,15</sup>

In the present study, the scavenged sampling technique was used to successfully develop a population PK model and new metronidazole dosing recommendations for preterm infants. The newly proposed PMA-based dosing regimen compared very favorably against published schemes<sup>5,6</sup>; a higher proportion (~90%) of subjects achieved the therapeutic target in simulated datasets. The PMA-based dosing scheme was particularly effective in more mature (30–32 weeks) and older (PNA >60 days) infants where suboptimal metronidazole concentrations were achieved when published guidelines were used in simulated datasets. To achieve higher concentrations in more mature infants, a cutoff of 34 weeks PMA was chosen to increase the dosing frequency in the PMA-based dosing regimen. This decision was based upon examination of the relationship between weight-adjusted CL and PMA (Fig. 3.4) where, at 34 weeks, the rate of change in metronidazole CL increased. A higher proportion of

subjects achieved the therapeutic target with the newly proposed regimen, while trough concentrations in each BGA group were similar to those observed with current routine medical care (Fig. 3.5). These data suggest that safety should not be different between the new dosing regimen and current clinical practice, but further prospective studies are warranted to verify this finding.

PMA-based dosing has proven successful in the evaluation of other therapeutics in preterm infants. A population PK study of 80 neonates with PMA 25–44 weeks demonstrated that PMA-based dosing of amikacin achieved the therapeutic target in over 90% of infants.<sup>9</sup> Similarly, PMA-based dosing was successful in 70 preterm infants (PMA 25–48 weeks) receiving vancomycin and 50 preterm infants treated with intravenous acetaminophen.<sup>7,8</sup>

Because the present study did not evaluate efficacy or clinical outcomes, a surrogate PD endpoint was used for the study population receiving metronidazole per routine clinical care and in simulated datasets. In this study, the majority of subjects (>70%) receiving metronidazole per routine medical care achieved the surrogate PD target for efficacy. In contrast, when dosing recommendations published in commonly used pediatric sources were used in simulated datasets, a lower proportion of subjects achieved the surrogate PD target. This finding may be due to higher doses (more frequent administration) prescribed per routine medical care when compared with published regimens and suggests that prescribing practices in the neonatal intensive care unit are not driven by these sources.<sup>5,6</sup>

In adults, metronidazole undergoes extensive hepatic metabolism with subsequent renal elimination<sup>16</sup>; the elimination half-life is 8 hours,<sup>17</sup> 20% is protein-bound, and the apparent  $V$  ranges between 0.25 and 0.85 L/kg.<sup>17</sup> The hepatic metabolizing and renal elimination systems undergo ontogenic changes during infancy, resulting in increased CL



with increasing size and age.<sup>18,19</sup> In young infants, metronidazole PK differs substantially from adults; the elimination half-life is 2–3-fold longer, and it decreases with increasing GA at birth and PNA.<sup>20–23</sup> Not surprisingly, in the present model, metronidazole CL increased proportionally with weight and disproportionately with PMA, and both covariates explained a substantial amount (~80%) of the CL IIV. This finding is consistent with prior observations in a metronidazole population PK study of 32 preterm infants (PMA 25–38 weeks) using dried blood spots (DBS) where body weight and PMA explained ~93% of the CL IIV.<sup>22</sup> The population PK parameter estimates in the present study are also comparable to those estimated in the DBS study. The CL estimate in a typical preterm infant with PMA 26 weeks in the present study was 0.014 L/h vs. 0.013 L/h in the DBS study. Similarly, CL estimates of a typical infant with PMA 32 weeks were 0.050 and 0.048 L/h, respectively. Estimates of population V in both studies were identical.<sup>22</sup> Other smaller, single-center studies have also shown similar associations between metronidazole CL and maturation and metronidazole V and weight.<sup>20,21</sup>

The addition of SCR into the multivariable CL model did not improve the goodness of fit, nor did it significantly explain remaining CL IIV. Due to ontogenic changes in renal function among preterm infants, SCR is strongly linked with maturational components such as PMA. This observation likely prevented our ability to discern the effect of the maturational component in CL IIV from SCR in the CL model-building process. The population PK model developed performed well during model evaluation and showed good precision around parameter estimates. After incorporation of weight as a covariate for V, the IIV estimate on V was close to zero. It is plausible that in the subjects enrolled in this study, weight explained all the IIV in V. It is also possible that the data were uninformative to

estimate the  $V_{IIV}$  due to a very narrow distribution of  $V_{IIV}$  resulting from sparse sampling.<sup>24</sup>

The bias introduced by scavenged sampling was quantified in this study and resulted in an underestimation of metronidazole concentrations by ~30%. This finding suggests that collecting scavenged samples from the clinical laboratory is a viable strategy to describe metronidazole PK and is further supported by the environmental stability of metronidazole for up to 48 hours.<sup>25</sup> However, during bootstrap procedures, imprecision was observed around the scavenged sample fixed parameter estimate (95% CI 10–42%). To more precisely estimate the amount of bias introduced by scavenged samples, a higher number of timed samples should be obtained. As expected, the residual variability (RV) estimated for scavenged samples was higher than that estimated for timed specimens. This finding could be due to higher documentation errors associated with sampling or dosing times extracted from the medical record after a scavenged sample was collected. In addition, information regarding the duration and conditions under which the samples remained in the clinical laboratory before freezing were not collected, which could add to the increased RV in scavenged samples.

In summary, the minimal-risk approach of scavenged PK sampling was an effective methodology to describe the population PK of metronidazole in preterm infants, to identify covariates that explain CL<sub>IIV</sub>, and to provide dosing recommendations in this population. After scaling for size, incorporating PMA as a covariate explaining CL<sub>IIV</sub> increased the model fit and led to a newly proposed, more simplistic dosing regimen based on PMA. Future efforts evaluating this methodology should consider the physicochemical properties of the drug (i.e., drug stability), more detailed documentation of sample collection and storage

conditions, and simultaneous collection of traditional plasma samples to fully assess the extent of bias introduced by scavenged sampling.

## References

1. Wade KC, Wu D, Kaufman DA, et al.; National Institute of Child Health and Development Pediatric Pharmacology Research Unit Network. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother.* 2008;52(11):4043–4049.
2. Uhari M, Seppänen J, Heikkinen E. Imipenem-cilastatin vs. tobramycin and metronidazole for appendicitis-related infections. *Pediatr Infect Dis J.* 1992;11(6):445–450.
3. Brook I. Bacteremia due to anaerobic bacteria in newborns. *J Perinatol.* 1990;10(4):351–356.
4. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs.* 2008;68(9):1227–1238.
5. Tschudy M, Arcara K. *The Harriet Lane Handbook: A Manual for Pediatric House Officers.* 19th ed. Philadelphia, PA: Mosby; 2011.
6. Thomson Reuters Clinical Editorial Staff. *Neofax 2011.* 24th ed. Montvale, NJ: Thomson Reuters; 2011.
7. Marqués-Miñana MR, Saadeddin A, Peris JE. Population pharmacokinetic analysis of vancomycin in neonates. A new proposal of initial dosage guideline. *Br J Clin Pharmacol.* 2010;70(5):713–720.
8. Palmer GM, Atkins M, Anderson BJ, et al. IV acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth.* 2008;101(4):523–530.
9. Sherwin CM, Svahn S, Van der Linden A, et al. Individualised dosing of amikacin in neonates: a pharmacokinetic/pharmacodynamic analysis. *Eur J Clin Pharmacol.* 2009;65(7):705–713.
10. Smith PB, Cohen-Wolkowicz M, Castro LM, et al.; Meropenem Study Team. Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. *Pediatr Infect Dis J.* 2011;30(10):844–849.
11. Cohen-Wolkowicz M, White NR, Bridges A, Benjamin DK Jr, Kashuba AD. Development of a liquid chromatography-tandem mass spectrometry assay of six antimicrobials in plasma for pharmacokinetic studies in premature infants. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011 Sep 22. [Epub ahead of print]

12. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet.* 1999;36(5):353–373.
13. Clinical and Laboratory Standards Institute. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard.* 7th ed. CLSI document M11-A7. Wayne, PA: CLSI; 2007.
14. Choonara I. Unlicensed and off-label drug use in children: implications for safety. *Expert Opin Drug Saf.* 2004;3(2):81–83.
15. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA.* 2003;290(7):905–911.
16. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy.* 1976;22(1):19–29.
17. Houghton GW, Smith J, Thorne PS, Templeton R. The pharmacokinetics of oral and intravenous metronidazole in man. *J Antimicrob Chemother.* 1979;5(5):621–623.
18. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth.* 2004;92(2):208–217.
19. de Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN. Pharmacokinetics and metabolism of oral midazolam in preterm infants. *Br J Clin Pharmacol.* 2002;53(4):390–392.
20. Hall P, Kaye CM, McIntosh N, Steele J. Intravenous metronidazole in the newborn. *Arch Dis Child.* 1983;58(7):529–531.
21. Jager-Roman E, Doyle PE, Baird-Lambert J, Cvejic M, Buchanan N. Pharmacokinetics and tissue distribution of metronidazole in the new born infant. *J Pediatr.* 1982;100(4):651–654.
22. Suyagh M, Collier PS, Millership JS, et al. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. *Pediatrics.* 2011;127(2):e367–374.
23. Upadhyaya P, Bhatnagar V, Basu N. Pharmacokinetics of intravenous metronidazole in neonates. *J Pediatr Surg.* 1988;23(3):263–265.

24. Baverel PG, Savic RM, Wilkins JJ, Karlsson MO. Evaluation of the nonparametric estimation method in NONMEM VI: application to real data. *J Pharmacokinetic Pharmacodyn.* 2009;36(4):297–315.
25. Menelaou A, Somogyi AA, Barclay ML, Bochner F. Simultaneous quantification of amoxicillin and metronidazole in plasma using high-performance liquid chromatography with photodiode array detection. *J Chromatogr B Biomed Sci Appl.* 1999;731(2):261–266.

Table 3.1. Dosing schemes used to assess pharmacodynamic target achievement

BW kg	GA weeks	PNA days	PMA weeks	Loading dose mg/kg	Maintenance dose mg/kg	Dosing interval hours
<i>The Harriet Lane Handbook</i>						
<1.2	NA	≥7	NA	NA	7.5	24
1.2–2	NA	≥7	NA	NA	7.5	12
≥2	NA	≥7	NA	NA	15	12
<i>Neofax</i>						
NA	NA	≤28	≤29	15	7.5	48
NA	NA	>28	≤29	15	7.5	24
NA	NA	≤14	30–36	15	7.5	24
NA	NA	>14	30–36	15	7.5	12
NA	NA	≤7	37–44	15	7.5	24
NA	NA	>7	37–44	15	7.5	12
NA	NA	ALL	≥45	15	7.5	6
<i>PMA-based dosing regimen</i>						
NA	≤32	NA	<34	15	7.5	12
NA	≤32	NA	34–40	15	7.5	8
NA	≤32	NA	>40	15	7.5	6

BW: birth weight; GA: gestational age; PMA: postmenstrual age; PNA: postnatal age.

Table 3.2. Clinical data by gestational age group

Characteristic	Gestational age at birth		
	<26 weeks	26–29 weeks	30–32 weeks
N	13	14	5
Gestational age, weeks	24 (22, 25)	28 (26, 29)	31 (30, 32)
Postnatal age, days	29 (2, 71)	32 (2, 78)	29 (10, 73)
Postmenstrual age, weeks	32 (24, 39)	32 (28, 43)	36 (32, 40)
Weight, g	1410 (678, 2537)	1510 (850, 3611)	1658 (1230, 3850)
Female sex	6 (46)	9 (64)	2 (40)
White race	4 (31)	10 (71)	2 (40)
Hispanic	1 (8)	2 (14)	0 (0)
Serum creatinine (mg/dL)	0.5 (0.3, 4.7)	0.5 (0.2, 1.2)	0.2 (0.1, 0.6)
Dose (mg/kg)	7.6 (4.2, 14.2)	7.8 (6.2, 15.1)	9.0 (6.5, 15.4)
Dosing frequency (h)	11.9 (5.9, 48.2)	12 (5.9, 48)	12.3 (11.2, 26.7)

Data are median (range) for continuous data and n (%) for categorical data.



Table 3.3. Model-building process

Base model and univariable analysis			
analysis	Population model	OFV	$\Delta$ OFV
V	$V = \theta_V X (wt/1.5)$	498	-
CL base model	$CL = \theta_{CL} X (wt/1.5)$	498	-
PMA	$CL = \theta_{CL} X (wt/1.5) X (PMA/32)^{\theta_{CL-PMA}}$	484.5	-13.5
PNA	$CL = \theta_{CL} X (wt/1.5) X (PNA/57)^{\theta_{CL-PNA}}$	486.4	-11.6
SCR	$CL = \theta_{CL} X (wt/1.5) X (0.5/SCR)^{\theta_{CL-SCR}}$	483.7	-14.3
SCR + indicator	$CL = \theta_{CL} X (wt/1.5) X (0.5/SCR)^{\theta_{CL-SCR} X CR}$	487.2	-10.8
Multivariable model			
CL, PMA, and SCR			
SCR	$CL = \theta_{CL} X (wt/1.5) X (PMA/32)^{\theta_{CL-PMA}} X (0.5/SCR)^{\theta_{CL-SCR}}$	480.8	-3.7

CL: clearance; OFV: objective function value; PMA: postmenstrual age; PNA: postnatal age; SCR: serum creatinine (mg/dL); V: volume of distribution; wt: weight (kg).

Table 3.4. Final population pharmacokinetic model parameter estimates

Parameter	Symbol	Point estimate	% RSE	Bootstrap CI		
				2.5%	Median	97.5%
CL (L/h)	$\theta_{CL}$	0.0397	10.9	0.0307	0.0398	0.0483
V (L)	$\theta_v$	1.07	15.0	0.85	1.12	1.37
CL, PMA	$\theta_{CL-PMA}$	2.49	29.8	1.01	2.57	4.20
SCAV	$\theta_{SCAV}$	0.713	12.3	0.581	0.721	0.899
Inter-individual variance						
CL (CV%)	$\omega^2_{CL}$	42.5	28.5	24.2	40.4	52.8
Residual variance (CV%)						
Blood draws	$\sigma_1^2$	13.5	24.5	0.3	13.3	15.7
Scavenged	$\sigma_1^2$	29.0	17.9	23.7	27.8	34.9

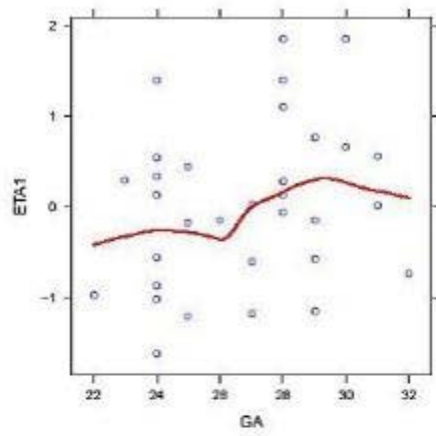
CI: confidence interval; CL: clearance; CV: coefficient of variation; PMA: postmenstrual age; RSE: relative standard error; V: volume of distribution.

Table 3.5. Individual empirical Bayesian pharmacokinetic parameter estimates by gestational age group

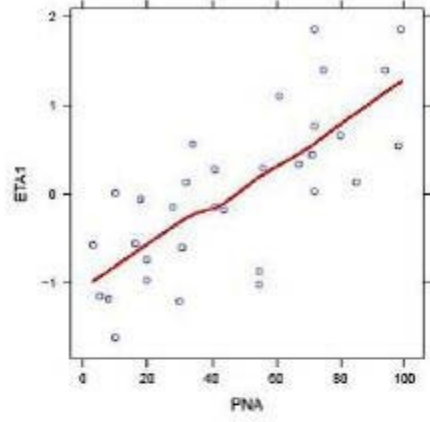
Gestational age	CL (L/h)	95% CI	CL (L/h/kg)	95% CI	V (L)	95% CI	V (L/kg)	95% CI	Half-life (h)	95% CI
<26 weeks	0.033	0.010, 0.187	0.024	0.010, 0.086	1.00	0.48, 1.81	0.71	NA	20.5	5.7, 49.9
26-29 weeks	0.040	0.012, 0.274	0.026	0.012, 0.076	1.08	0.60, 2.58	0.71	NA	18.6	6.5, 38.7
30-32 weeks	0.071	0.019, 0.285	0.029	0.015, 0.074	1.18	0.88, 2.75	0.71	NA	16.7	6.7, 31.1
Overall	0.041	0.012, 0.274	0.025	0.012, 0.076	1.06	0.54, 2.58	0.71	NA	19.1	6.5, 38.7

CI: confidence interval; CL: clearance, V: volume of distribution.

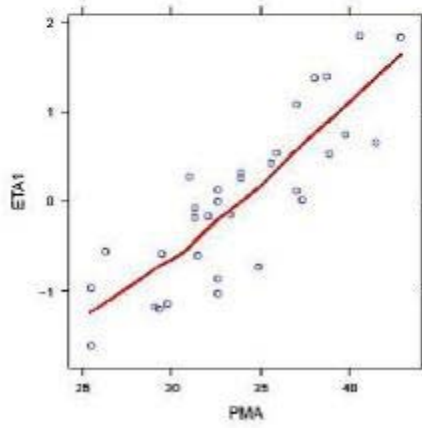
Fig. 3.1. Base model scatter plots of CL ETA1 estimates and the following: BGA (A), PNA (B), PMA (C), and SCR (D).



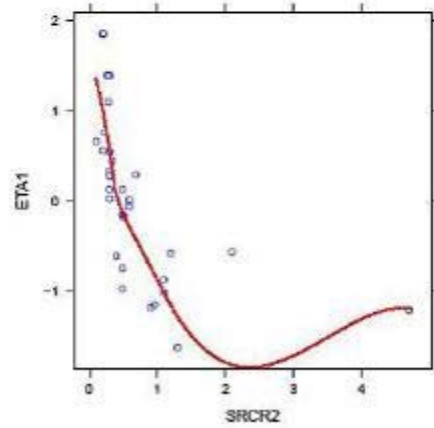
A



B



C



D

Fig. 3.2. Final population PK model diagnostic plots: observed vs. population predictions (A) and individual predictions (B); weighted residuals vs. population predictions (C) and time (D). For A and B, the line of identity is included as a reference. For weighted residuals, a solid line at  $y=0$  is included as a reference.

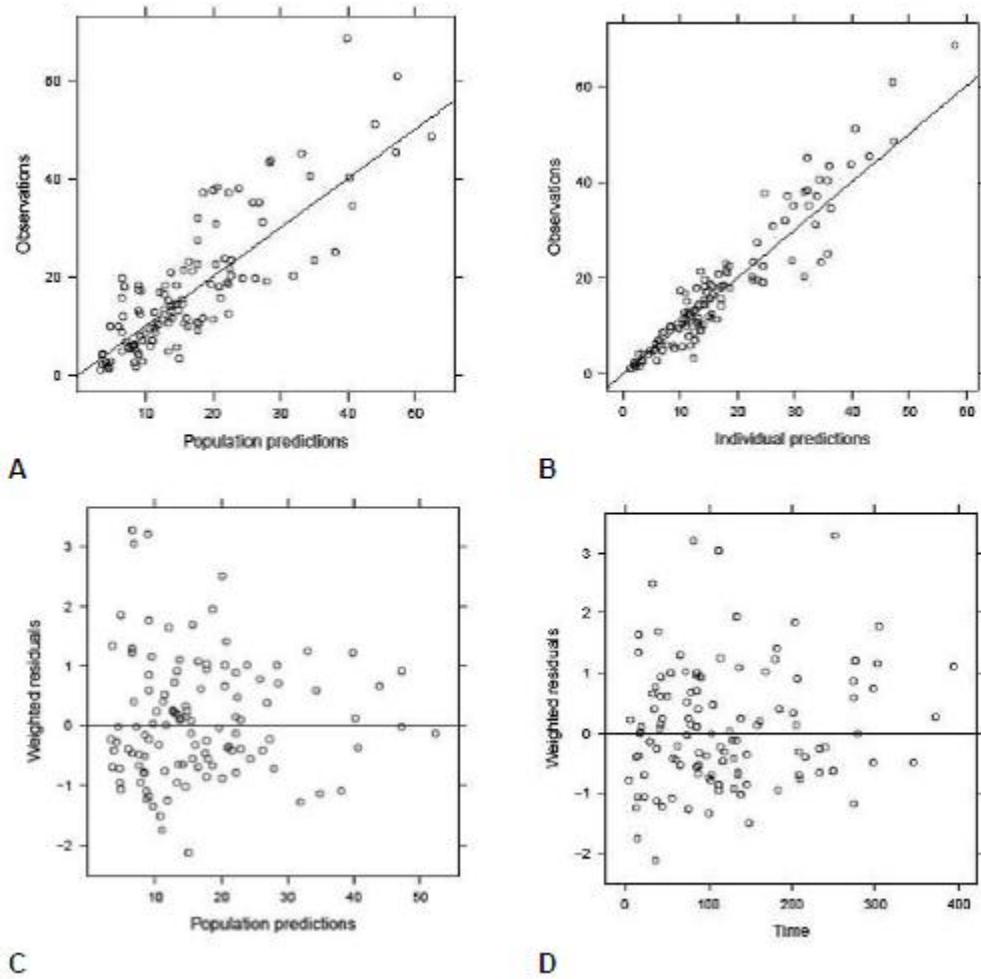


Fig. 3.3. Visual predictive check of metronidazole concentrations versus time. Solid black circles represent observed concentrations. Shaded gray area represents the 90% prediction interval. Solid and dashed black lines represent observed and predicted median concentrations, respectively.

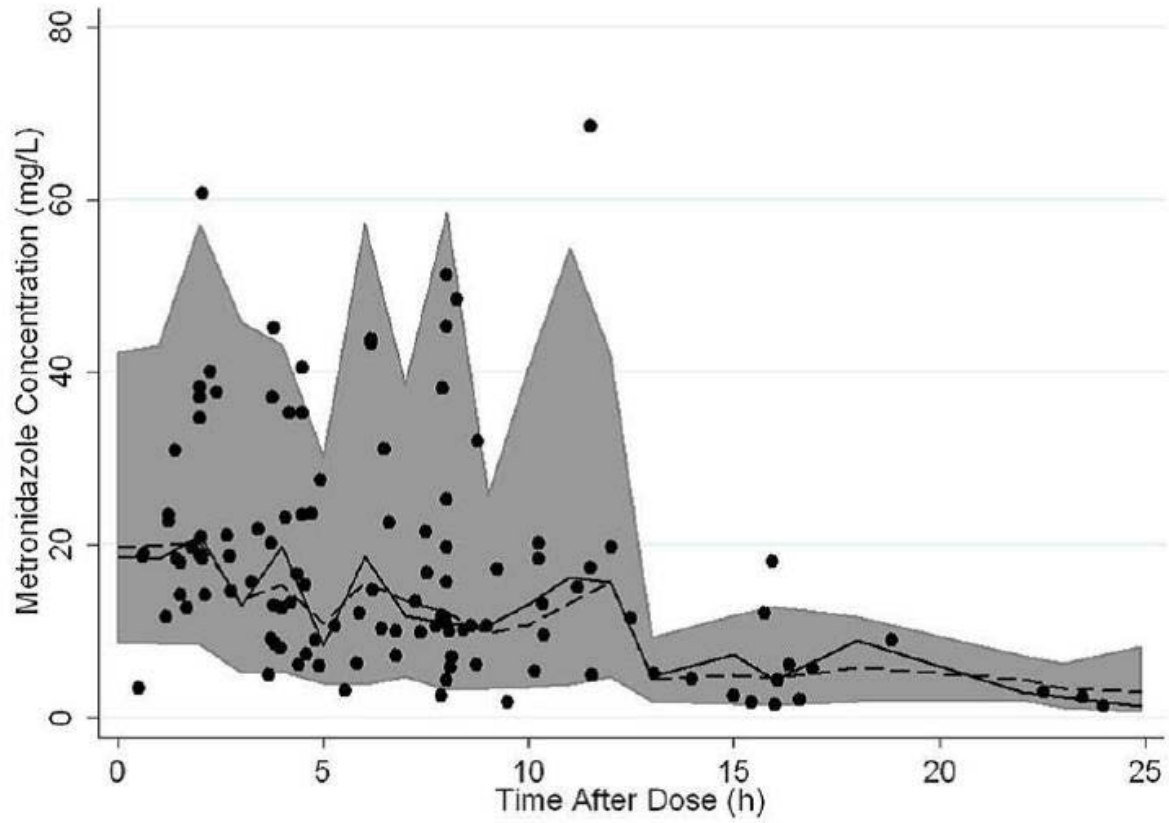
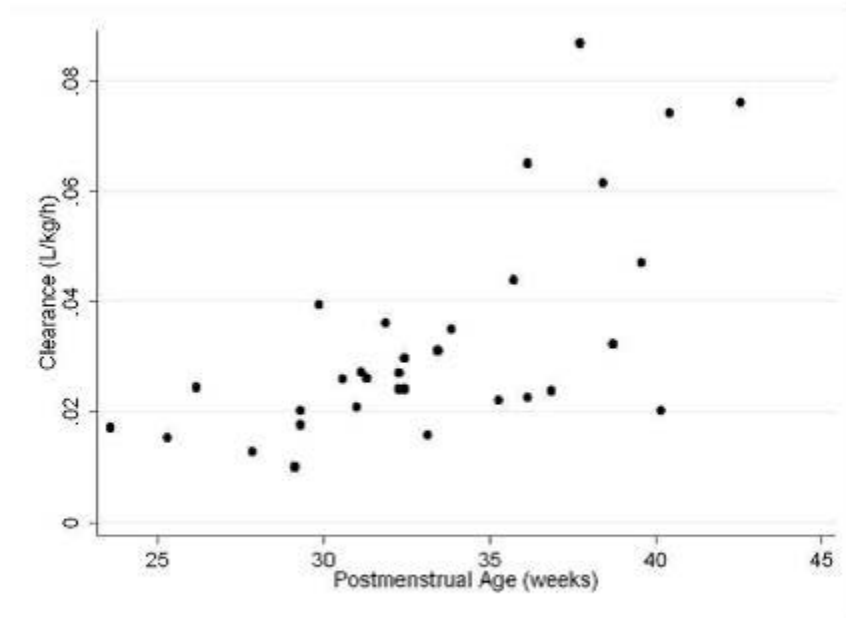
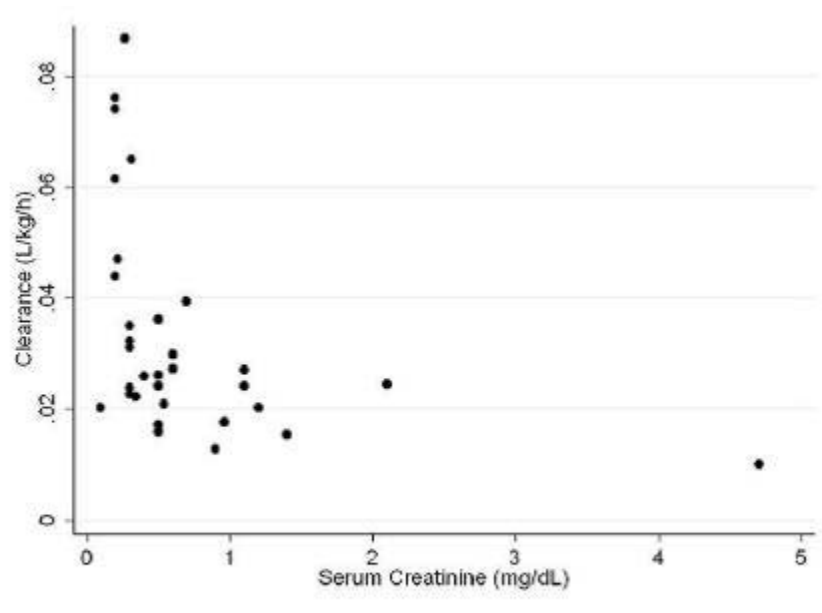


Fig. 3.4. Weight-normalized metronidazole clearance versus postmenstrual age (A) and serum creatinine (B).

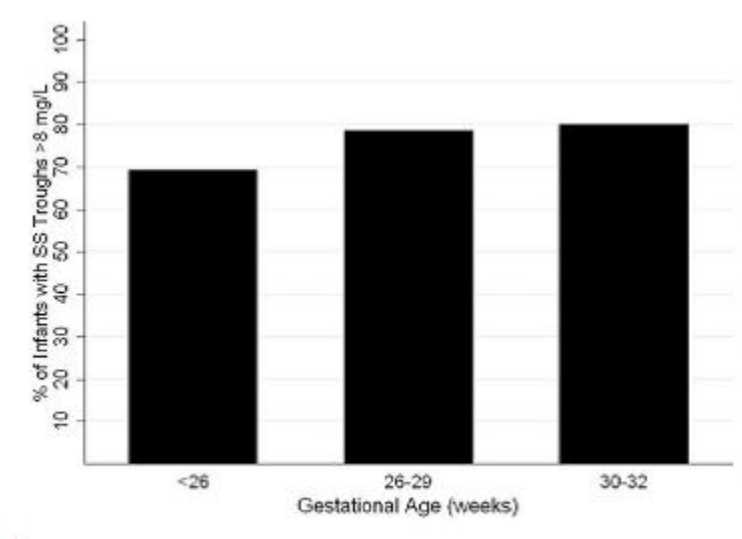


A

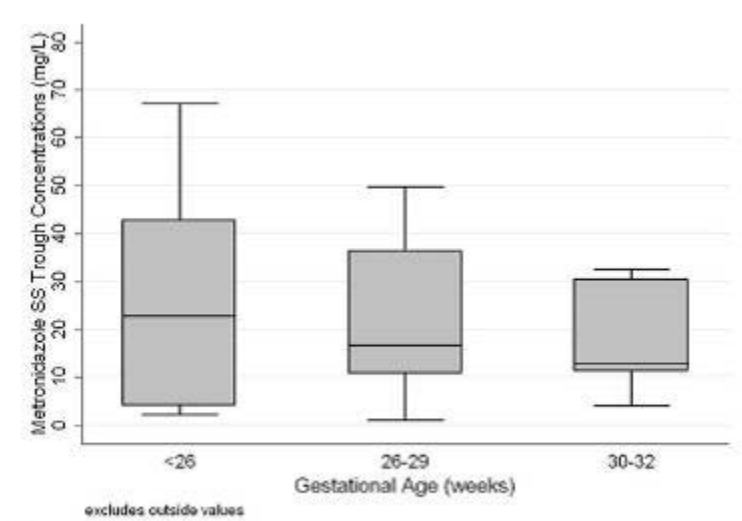


B

Fig. 3.5. PD target attainment rates by gestational age group: proportion of study subjects who met PD target with dosing prescribed per routine medical care (A); predicted steady-state metronidazole trough concentrations in study subjects (B); proportion of simulated subjects who met PD target with different dosing schemes (C); and predicted steady-state metronidazole trough concentrations in simulated subjects (D). Red line represents 80% success rate. HL: Harriet Lane; PMA: postmenstrual age dosing regimen.

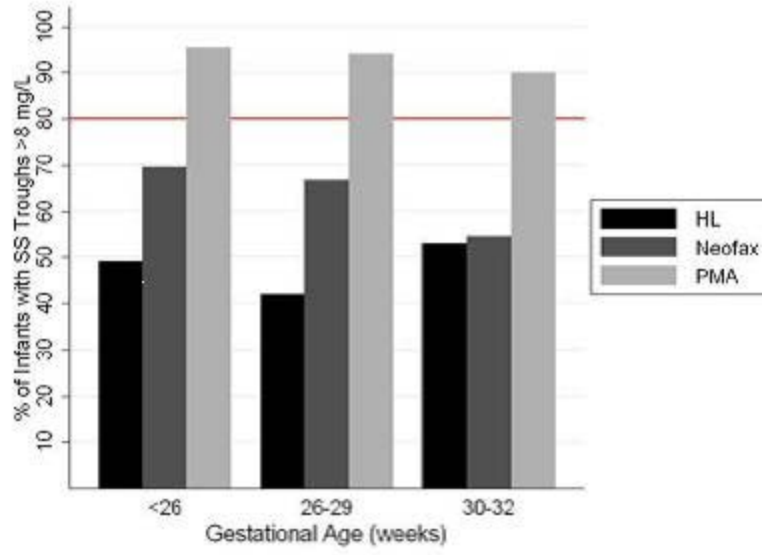


A

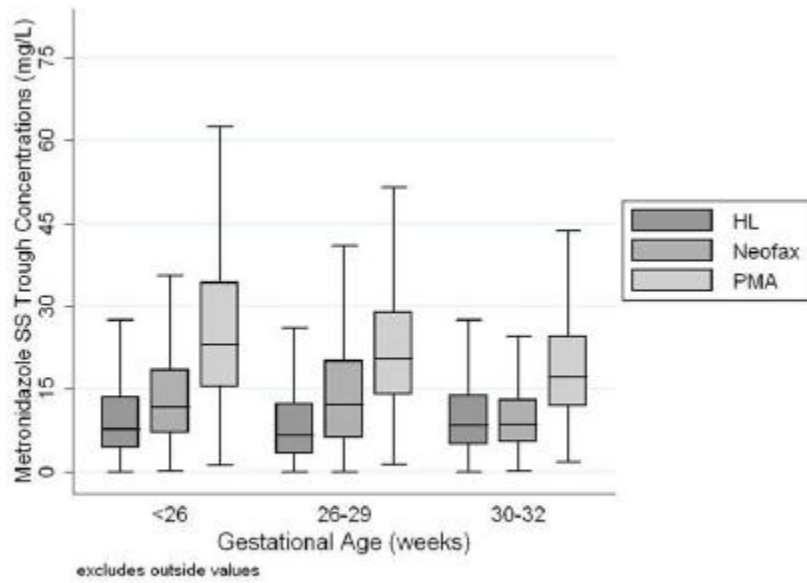


B



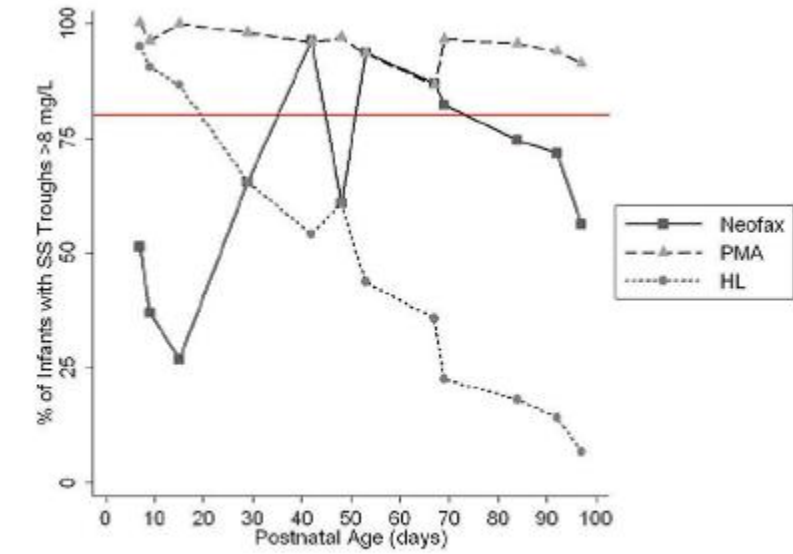


**C**

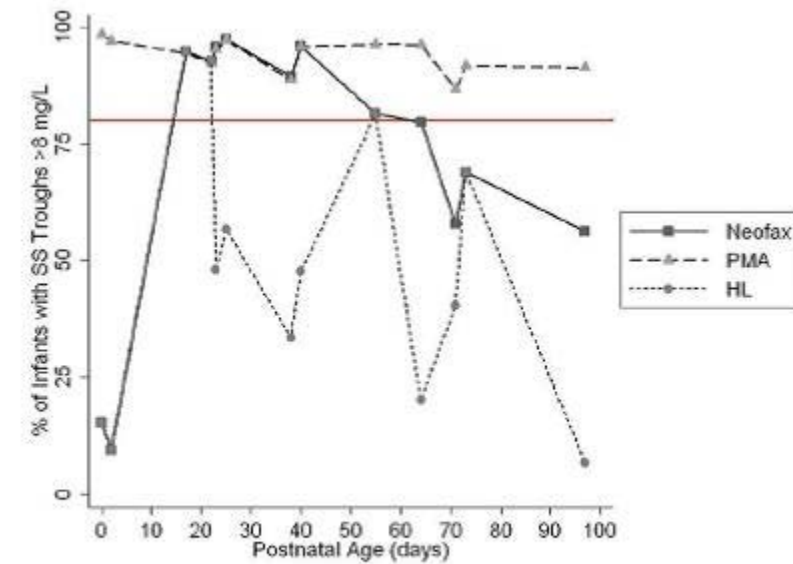


**D**

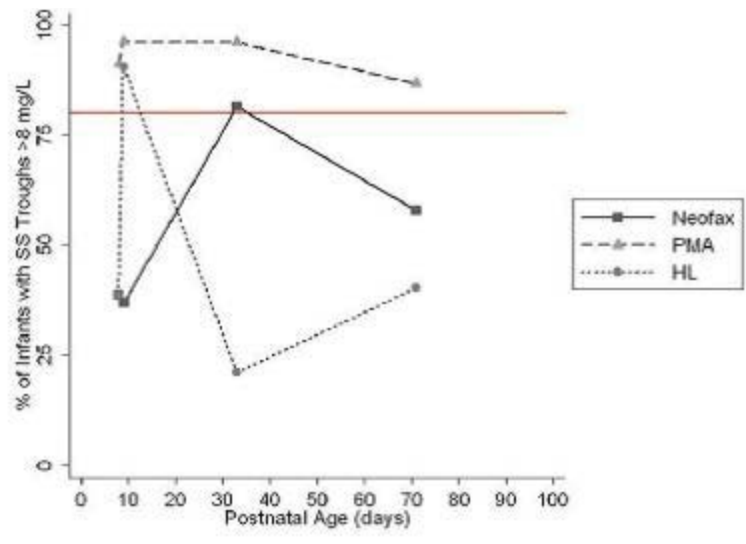
Fig. 3.6. PD target attainment rates by gestational age group and postnatal age in simulated subjects: GA group <26 weeks (A); GA group 26–29 weeks (B); GA group 30–32 weeks (C). Red line represents 80% success rate. HL: Harriet Lane; PMA: postmenstrual age dosing regimen.



**A**

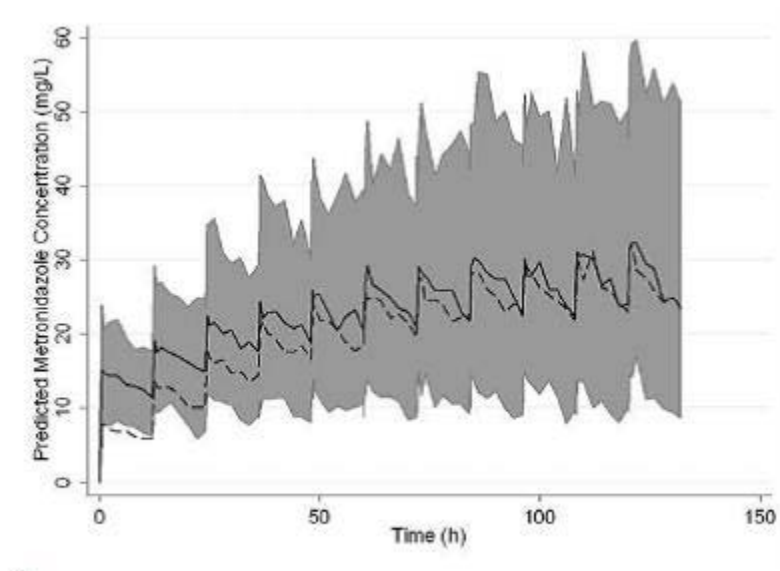


**B**

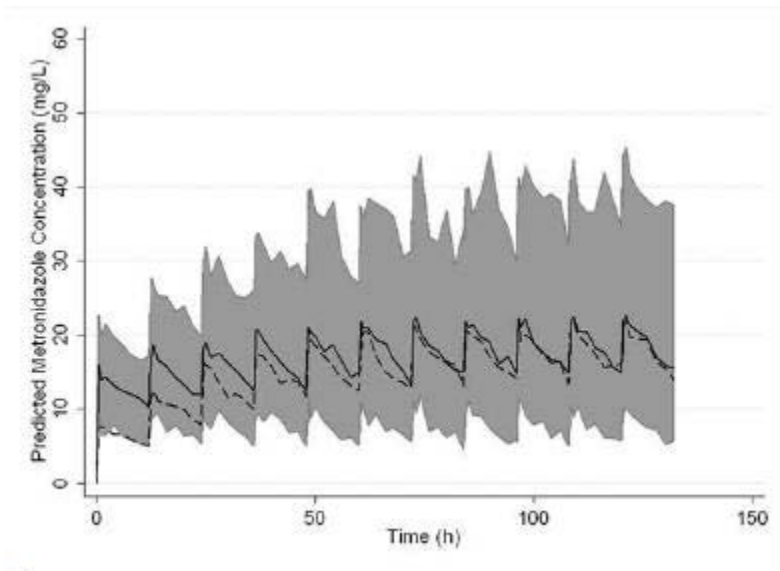


C

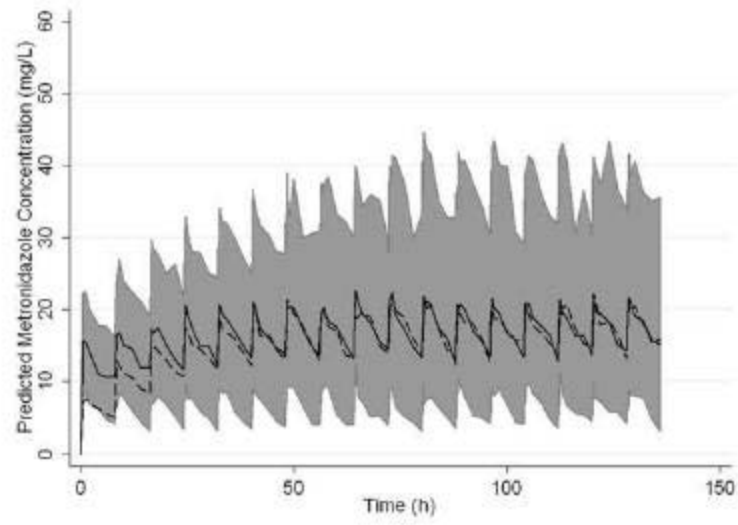
Fig. 3.7. Simulated time-concentration profiles with proposed PMA dosing regimen in typical subjects: PMA 26 weeks, weight 900 g (A); PMA 32 weeks, weight 1900 g (B); PMA 36 weeks, weight 2800 g (C); PMA 41 weeks, weight 3800 g (D). Shaded gray area represents the 90% prediction interval around the loading dose simulations. Solid and dashed black lines represent loading vs. no loading dose predicted median concentrations, respectively.



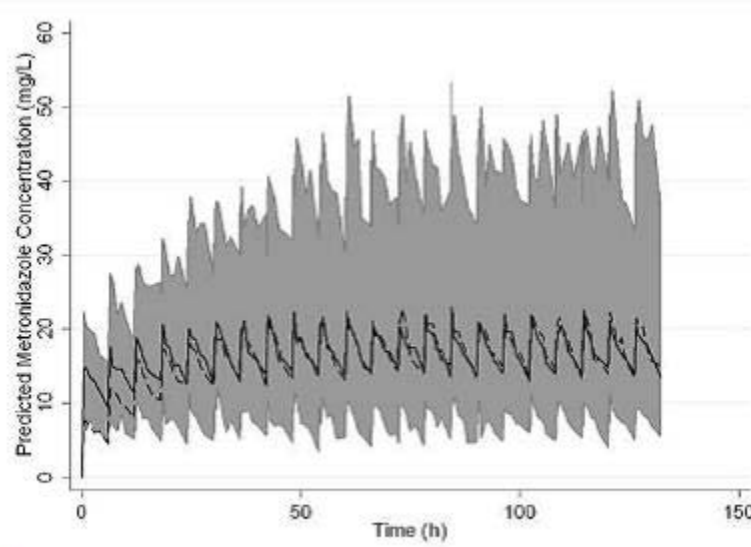
**A**



**B**



C



D

## CHAPTER 4: PIPERACILLIN AND TAZOBACTAM IN DRIED BLOOD SPOTS: ASSAY DEVELOPMENT AND CLINICAL APPLICATION IN PRETERM INFANTS

### Introduction

Pharmacokinetic (PK) studies in preterm infants are exceptionally scarce due to the challenges associated with traditional clinical trial design in this vulnerable population. These challenges include low rates of informed consent among parents of critically ill infants; lack of availability of sensitive drug concentration assays; and limited blood volume necessary to conduct PK studies. These limitations have forced investigators to rely on the extrapolation of PK data obtained in older children and adults to estimate PK parameters and provide dosing recommendations in preterm infants. However, this approach underestimates the complicated physiology of preterm infants, which differs greatly from other populations. Preterm infants have a larger extracellular fluid volume, immature renal and hepatic function, underdevelopment of metabolic enzymatic systems, and a unique blood-brain barrier—all of which can substantially alter drug disposition.<sup>1</sup>

Dried blood spot (DBS) sampling is an established technology used globally in neonatal screening. The DBS sampling method involves the collection of 15–30  $\mu$ L of whole blood on blotting paper. Given the small blood volumes required for DBS sampling, this technology has emerged as an attractive tool in pre-clinical and clinical PK studies.<sup>2,3</sup> In addition, DBS sampling appeals to the pediatric research community as a potential tool for overcoming blood volume limitations in this population. However, the use of DBS in

pediatric clinical trials is extremely scarce; only 1 study using DBS technology in preterm infants has been published.<sup>3</sup> This could be the result of a lag time in adopting emerging technologies, as well as a lack of DBS assay development for drugs commonly used in children. The present study describes the development of a liquid chromatography-tandem mass spectrometry (LC–MS/MS) assay of piperacillin and tazobactam in DBS and its application to clinical samples collected from preterm infants.

## Methods

### *Chemicals and reagents*

Piperacillin and dicloxacillin (internal standard [IS]) were purchased from the Sigma Chemical Company (St. Louis, MO, USA). Tazobactam was purchased from the U.S. Pharmacopeia (Rockville, MD, USA). High-performance liquid chromatography (HPLC)-grade chemicals were purchased from Fisher Scientific (Norcross, GA, USA). Purified compressed nitrogen was obtained from Airgas-National Welders (Charlotte, NC, USA). Drug-free pooled whole blood was obtained from Biological Specialty Corporation (Colmar, PA, USA). Whole blood was anticoagulated with potassium tri-phosphate ethylenediaminetetraacetic acid (EDTA).

### *Equipment*

Compounds were analyzed with a triple quadrupole mass spectrometer API 4000 (Applied Biosystems–ABSciex, Foster City, CA, USA). A Shimadzu solvent delivery system (Columbia, MD, USA), LEAP HTC PAL thermostatted autosampler (Carrboro, NC, USA), Valco switching valve (Houston, TX, USA), and Analyst Software version 1.4.1 (Applied

Biosystems–ABSciex, Foster City, CA, USA) run on a Dell desktop computer (operated by Windows XP professional) were used for this method. DMPK FTA Type-C cards (Whatman, GE Healthcare, Kent, UK) and Harris Uni-Core 6.0 MM punchers were purchased from Fisher Scientific (Norcross, GA, USA).

### *Preparation of standards*

Individual clear stock solutions of piperacillin and tazobactam were prepared at a concentration of 15 mg/mL. Each analyte was accurately weighed and dissolved in 1 mL of dimethyl sulfoxide (DMSO). The master stock solution was prepared as a composite of the 2 compounds (0.5 mL each), adjusted to a final concentration of 1,500,000 ng/mL for each analyte by 4.0 mL of DMSO. This master stock standard was used to prepare 7 intermediate composite stock solutions: piperacillin (1,500,000, 750,000, 300,000, 150,000, 30,000, 15,000, and 3,000 ng/mL) and tazobactam (750,000, 300,000, 150,000, 30,000, 15,000, 3,000, and 1,500 ng/mL).

Whole blood working calibration solutions at 150,000, 75,000, 30,000, 15,000, 3,000, 1,500, and 300 ng/mL for piperacillin and 75,000, 30,000, 15,000, 3,000, 1,500, 300, and 150 ng/mL for tazobactam were prepared by diluting the intermediate solutions in human drug-free fresh whole blood in a ratio of 1:9. Twenty-five microliters of each working calibration solution were spotted onto DMPK FTA Type-C cards and left to dry for 4 hours. From the master and intermediate stock solutions, quality control (QC) intermediate stock solutions were prepared in DMSO at concentrations of 9,000, 600,000, and 1,200,000 ng/mL for piperacillin and 4,500, 180,000, and 600,000 ng/mL for tazobactam. Whole blood working QC samples of 900, 60,000, and 120,000 ng/mL for piperacillin and 450, 18,000, and 60,000



ng/mL for tazobactam were prepared by diluting the QC intermediate solutions in human drug-free fresh whole blood in a ratio of 1:9. Twenty-five microliters of each working QC solution were spotted onto DMPK FTA Type-C cards and left to dry for 4 hours.

#### *Internal standard preparation*

Dicloxacillin (1 mg) was weighed and dissolved in DMSO to achieve a final concentration of 1.0 mg/mL (stock solution). The IS working solution was prepared by diluting 0.3 mL of this solution in 75% methanol:water to achieve a final concentration of 3,000 ng/mL.

#### *Samples and pre-treatment*

This method was used to measure antimicrobial concentrations in clinical samples collected from preterm infants. Sample collection (~1 drop onto card) occurred under an investigational protocol approved by the institutional review board at participating sites and after informed consent was obtained from caregivers of study participants. Samples were obtained at the same time as plasma samples and could be obtained after single or multiple dosing. DBS samples were left out to dry for up to 4 hours, were placed in a zip-lock bag including a desiccant and humidity indicator, and then were transferred to a  $-80^{\circ}\text{C}$  temperature-monitored freezer for storage until analysis. DBS samples were collected from intravascular devices, venipunctures, arterial sites, or capillary heel sticks. Prior to extraction, all DBS cards were brought to room temperature for 2 hours and all cards were photographed using a digital camera. DBS samples were compared with paired plasma samples that were previously analyzed with a validated method.<sup>4</sup> Two independent observers classified each

DBS sample into 2 categories, valid and non-valid. Criteria for a non-valid samples included appearance of multiple drops of blood per each spot on the card, asymmetry of spot, and cross-contamination between spots on the same card. The ratio of DBS/plasma concentration ratio was calculated for each sample for both compounds. The correlation between DBS and plasma concentrations was assessed with scatter plots and weighted (variance of y) linear regression. Hematocrit (Hct) values were recorded for each participant if collected during routine medical care. Hct values obtained prior to sample collection were carried forward if the value was missing at the time of DBS sample collection.

#### *The extraction procedure*

On the day of analysis, 6 mm out of the center of 1 spot from each DBS card was punched into a 2.0 mL labeled conical plastic Eppendorf tube. Two hundred microliters of internal standard in 75% methanol:water was added into the Eppendorf tube containing the punched DBS sample. The solutions were gently vortex-mixed for 10 minutes and centrifuged at 15,600 g at 4° C for 5 minutes. The supernatant portion was transferred into a 96-insert holder with 0.7 mL glass inserts (Q Glass, Towaco, NJ, USA). The inserts on the holder were tightly sealed with a silicone 96-insert cover.

#### *LC-MS/MS analysis*

Piperacillin was analyzed in positive mode and tazobactam was analyzed in negative mode during a separate injection run from the same glass insert. Dicloxicillin was used as internal standard for both positive and negative analyses. The injection volume was 4 µL. Chromatography was achieved by using a reverse-phase C18 Aquasil column (50 x 2.1-mm

internal diameter, 5 µm particle size; Thermo Fisher, Waltham, MA, USA) with a flow rate of 0.75 ml/min for analysis in positive mode and a C18 Ultra Aqueous column (50 x 2.1-mm internal diameter, 3 µm particle size; Restek, Bellefonte, PA, USA) with a flow rate of 0.35 ml/min for analysis in negative mode. In both analyses, mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in methanol. The chromatographic separation of analytes was performed with gradient elution of increasing mobile phase B (0% hold until 0.7 minutes, 0–15% from 0.7–1 minute, 15–100% from 1–4 minutes, 100% hold from 4–4.5 minutes, 0% from 4.5–6 minutes for positive mode; 0% hold until 0.7 minutes, 0–100% from 0.7–2.5 minutes, 100% hold from 2.5–3.5 minutes, 0% from 3.5–5 minutes for negative mode). Flow was diverted to waste for the first 0.7 minutes and after 4 minutes. Total run time was 6 and 5 minutes for positive and negative mode, respectively.

MS/MS analysis was performed on a triple quadrupole mass spectrometer API 4000 (Applied Biosystems–ABSciex, Foster City, CA, USA) operated with electrospray ionization (TurboV source using the electrospray probe). Ionspray voltage and turbo heater temperature were kept at 2500 V (-2000 V for tazobactam) and 500° C, respectively. Compound-specific instrument parameters were optimized for each transition (Table 4.1) to obtain the most robust signal.

#### *Linearity, limit of quantification, and limit of detection*

Linearity was assessed using 5 calibration curves analyzed on 3 separate days. For validation, each point on the calibration curve was run in duplicate (2 separate extractions), and the curves were constructed by calculating the peak area ratios of each compound to the

internal standard and plotting these against the nominal concentration of the sample. Back-calculated calibration concentrations were determined using several models. The calibration curve with the best accuracy and precision throughout the curve range was considered the best fit. Quadratic regression of the ratio of compound to IS concentration (x) versus peak area ratio of compound to IS (y) using a  $1/(x)$  weighting scheme was used for calculations because it provided the best fit to the data.

The upper limit of quantification (ULOQ) was defined as the highest standard concentration for which both the relative standard deviation and the percent deviation from the nominal concentration were less than 15%.<sup>6</sup> The lower limit of quantification (LLOQ) was defined as the lowest concentration for which both the relative standard deviation and the percent deviation from the nominal concentration were less than 20%.

#### *Accuracy, precision, and recovery*

Accuracy and precision of the analytical method was quantified using 4 concentrations of QC samples (including LLOQ) run 6 times (6 separate extractions) in sequence on 3 different days (total of 18 replicates for each concentration). In addition, accuracy and precision of diluted samples were determined. Dilutions (1:1, 1:3, and 1:9 ratios) of a highly concentrated piperacillin solution (300,000 ng/mL) were performed after the extraction process with extract from blank DBS samples. The calculated concentrations were compared to the nominal concentrations. Recovery was calculated from peak area responses of 2 solutions (A and B). Solution A was the extract of a 25  $\mu$ L DBS QC extracted using the extraction solvent (75% methanol:water). Solution B contained the extract of 25  $\mu$ L blank DBS extracted using the extraction solvent (75% methanol:water) containing piperacillin and tazobactam at concentrations equal to the nominal QC values. Recovery (%)

was determined as  $A/B \times 100$ , and the following QC concentration levels were used: 12,500 ng/mL, 25,000 ng/mL, and 50,000 ng/mL. The whole blood spot (rather than a 6 mm punch) was used to estimate recovery.

### *Stability*

To test stability of analytes during the DBS card drying process, samples were left at room temperature for up to 4 hours prior to extraction. DBS samples were extracted in duplicates at the following time points: 15, 30, 120, and 240 minutes. Mean peak areas of each analyte were plotted over time to assess changes in peak areas with time.

## Results

### *Linearity*

The calibration curve was calculated using peak area ratio values at 7 standard concentrations. A quadratic regression provided the best fit to the data. The data for the calibration curves ( $n=3$ ) are shown in Table 4.2, along with the mean  $\pm$  standard deviation of 3 standard curve quadratic coefficients, slopes, intercepts, and correlation coefficients ( $r^2$ ). The regression coefficient ( $r^2$ ) for all calibration curves was greater than 0.9965.

### *The limit of quantification*

The LLOQ for piperacillin was 300 ng/mL and for tazobactam 150 ng/mL, and the ULOQ for piperacillin was 150,000 ng/mL and for tazobactam 75,000 ng/mL.

Chromatograms of blank, LLOQ, and ULOQ samples are shown in Fig. 4.1 and Fig. 4.2.

### *Accuracy, precision, and recovery*

The results of the accuracy and precision experiments at 4 different QC levels for piperacillin and 3 QC levels for tazobactam are shown in Table 4.3. Within-day accuracy of both analytes ranged from 96–112%, with a mean of 103%. Between-day accuracy of both analytes ranged from 96–110%, with a mean of 103%. Within- and between-day coefficient of variations varied from 4.3–9.7% and 5.4–10.3%, respectively. Overall, results indicate that the method was accurate and precise for both compounds. In addition, piperacillin concentration measurements of partially diluted samples were accurate and precise across all dilution ratios (Table 4.4). The greatest percent deviation for all diluted samples was 11.5% when diluted 1:9. The greatest percent coefficient of variation for all diluted samples was 5.6%. The absolute recovery of all compounds at all concentrations was greater than 79% for piperacillin and 65% for tazobactam (Table 4.2).

### *Stability*

Peak area changes were not observed during the DBS card drying process for piperacillin and tazobactam (Fig. 4.3). Piperacillin and tazobactam response (peak area) was slightly lower (<15%) at 15 minutes when compared with later time points.

### *Analysis of patient samples*

The applicability of the described method was evaluated by analyzing DBS samples (N=56 total, 47 with paired plasma) collected from premature infants given multiple intravenous doses of piperacillin-tazobactam. Ten samples were identified as non-valid due to the presence of multiple drops of blood per each spot on the card and cross-contamination between cards; 37 sample pairs were included in the analysis. The median (5, 95%)

piperacillin concentrations in plasma and DBS were 107.0 (15.4, 249.0) mg/L and 49 (11.9, 103) mg/L, respectively; and for tazobactam 12.2 (1.94, 26.4) mg/L and 5.8 (1.02, 13.3) mg/L, respectively. The DBS-to-plasma concentration ratio for piperacillin and tazobactam can be seen in Table 4.5. The overall median ratio of piperacillin DBS-to-plasma ratio was 0.37 (range, 0.20, 3.01) and for tazobactam was 0.50 (0.21, 1.41). A strong association was observed between DBS and plasma concentrations for both piperacillin and tazobactam ( $r^2=0.81$  and  $0.80$ , respectively;  $p<0.001$ ) (Fig. 4.4). No trends were observed between the piperacillin and tazobactam DBS-to-plasma ratios and the range of plasma concentrations (Fig. 4.4).

## Discussion

The method described successfully measures drug concentration of piperacillin and tazobactam in DBS samples. Other investigators have successfully measured antimicrobials in DBS, including antiretroviral, antimalarial, and anti-tuberculous drugs<sup>7-9</sup>; however, this is the first report of DBS sample analysis of a beta-lactam antibiotic. The ability to measure drug concentrations of antimicrobials in DBS samples is an important milestone in evaluating drug disposition in preterm infants. This method involves a very simple extraction process and a short run time ideal for high throughput application. In addition, DBS clinical samples required an 8-fold lower blood volume than traditional PK plasma samples, virtually no sample processing, and convenient storage. The combination of these factors makes DBS sampling an ideal matrix for PK analysis in preterm infants. Also, piperacillin and tazobactam demonstrated on-card stability throughout the drying process. Peak area for both analytes was slightly lower at 15 minutes when compared with later time points, which could

have resulted from incompletely dried sample at 15 minutes and potential analyte hydrolysis. In addition to the benefits described above, the comparison of DBS (whole blood) drug concentrations to plasma of preterm infants provides new insights into the red blood cell partition of drugs in this population. Partition of drugs into red blood cells is usually evaluated during drug development using in vitro techniques under controlled conditions or in healthy volunteers.<sup>10</sup> However, extrapolation of these findings to in vivo physiology is controversial because red blood cell partition is dependent on blood pH, temperature, and protein binding, which can behave differently in vivo. An example of this discrepancy was evident during the evaluation of phenobarbital red blood cell partitioning in neonates and their mothers. In neonates, phenobarbital partitioning was lower relative to their mothers.<sup>11</sup> Because phenobarbital binds to hemoglobin, this finding suggested a different affinity of phenobarbital to fetal hemoglobin present at birth.

Piperacillin and tazobactam concentrations in DBS samples were strongly associated with measurements in plasma samples; overall, DBS piperacillin and tazobactam concentrations were lower than plasma. This was evidenced by median DBS-to-plasma concentration ratios of 0.37 and 0.50 for piperacillin and tazobactam, respectively. This difference is not unexpected given the assumption that piperacillin and tazobactam do not partition into red blood cells.<sup>12</sup> In this setting, the red blood cells in DBS samples act as a diluent resulting in lower DBS drug concentrations. Consequently, the difference between the DBS-to-plasma ratio and unity should approach the hematocrit value, as was evident for both drugs. In some cases, however, the DBS-to-plasma ratio for piperacillin was lower than expected even after consideration of hematocrit. This was more evident at higher (>150 mg/L) piperacillin plasma concentrations. It is plausible that piperacillin degraded at room



temperature<sup>13</sup> during the DBS sample drying process. However, unless clinical samples were left to dry for periods longer than 4 hours, drug degradation is unlikely given our stability results during a 4-hour period. It is also possible that DBS measurements had measurement errors related to inconsistency in sample collection techniques across sites and use of multiple blood sources (i.e., with and without anticoagulant) before spotting on the card. The presence of EDTA in clinical samples has been shown to produce ion enhancement of certain compounds.<sup>14</sup> Inconsistency in sample collection technique could also account for the degree of variability seen in DBS-to-plasma concentration ratios for both drugs. Even though the DBS-to-plasma ratio for both drugs suggested little to no partitioning into red blood cells, there are no published reports addressing this question. Future studies are required to confirm these findings.

We successfully developed a method to simultaneously assay piperacillin and tazobactam in DBS samples. The assay was validated with respect to accuracy, precision, limit of detection, recovery, and stability, and has been successfully applied to clinical samples from preterm infants. This method has many clinical applications within the field of pediatrics, as it is simple, highly sensitive and specific, and requires ultra-low volumes of clinical samples. DBS and plasma piperacillin and tazobactam concentrations were highly correlated and on average, piperacillin and tazobactam DBS concentrations were lower than plasma. This difference suggests that piperacillin and tazobactam do not partition into red blood cells. These data suggest that DBS samples can be used as a surrogate for piperacillin and tazobactam plasma concentrations.

## References

1. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–1167.
2. Spooner N, Lad R, Barfield M. Dried blood spots as a sample collection technique for the determination of pharmacokinetics in clinical studies: considerations for the validation of a quantitative bioanalytical method. *Anal Chem*. 2009;81(4):1557–1563.
3. Suyagh M, Collier PS, Millership JS, et al. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. *Pediatrics*. 2011;127(2):e367–374.
4. Cohen-Wolkowicz M, White NR, Bridges A, Benjamin DK Jr, Kashuba AD. Development of a liquid chromatography-tandem mass spectrometry assay of six antimicrobials in plasma for pharmacokinetic studies in premature infants. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2011 Sep 22. [Epub ahead of print]
5. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. *Lancet*. 1995;346(8982):1085–1087.
6. Shah VP, Midha KK, Findlay JW, et al. Bioanalytical method validation--a revisit with a decade of progress. *Pharm Res*. 2000;17(12):1551–1557.
7. Cheomung A, Na-Bangchang K. HPLC with ultraviolet detection for the determination of chloroquine and desethylchloroquine in whole blood and finger-prick capillary blood dried on filter paper. *J Pharm Biomed Anal*. 2011;55(5):1031–1040.
8. Meesters RJ, van Kampen JJ, Reedijk ML, et al. Ultrafast and high-throughput mass spectrometric assay for therapeutic drug monitoring of antiretroviral drugs in pediatric HIV-1 infection applying dried blood spots. *Anal Bioanal Chem*. 2010;398(1):319–328.
9. Vu DH, Koster RA, Alffenaar JW, Brouwers JR, Uges DR. Determination of moxifloxacin in dried blood spots using LC-MS/MS and the impact of the hematocrit and blood volume. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2011;879(15–16):1063–1070.
10. Vidrequin S, Gimenez F, Basco LK, et al. Uptake of mefloquine enantiomers into uninfected and malaria-infected erythrocytes. *Drug Metab Dispos*. 1996;24(6):689–691.
11. Wallin A, Herngren L. Distribution of phenobarbital in whole blood during pregnancy and perinatally—an in vitro study. *Eur J Clin Pharmacol*. 1985;29(2):187–191
12. Sörgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J Antimicrob Chemother*. 1993;31 Suppl A:39–60.

13. Arzuaga A, Isla A, Gascón AR, et al. Quantitation and stability of piperacillin and tazobactam in plasma and ultrafiltrate from patients undergoing continuous venovenous hemofiltration by HPLC. *Biomed Chromatogr.* 2005;19(8):570–578.
14. Pranger AD, Alffenaar JW, Wessels AM, Greijdanus B, Uges DR. Determination of moxifloxacin in human plasma, plasma ultrafiltrate, and cerebrospinal fluid by a rapid and simple liquid chromatography- tandem mass spectrometry method. *J Anal Toxicol.* 2010;34(3):135–141.

Table 4.1. Optimal precursor and product ions and instrument parameters by compound

	Molecular weight (g/mol)	Ionization mode	Precursor ion	Product ion	Collision gas	Collision energy (eV)
Piperacillin	517.55	Positive	518.2	143.2	10	25
Tazobactam	300.29	Negative	299.0	137.9	10	-20
Dicloxacillin						20
(IS)	470.32	Positive	470.1	160.1	10	
Dicloxacillin						-20
(IS)	470.32	Negative	468.0	326.8	10	

IS: internal standard.

Table 4.2. Summary of standard curve, retention times, and extraction efficiency

Range <i>ng/mL</i>	Standard curve							Extraction efficiency %	Mean deviation %
	$r^2$	Quadratic coefficient	SD	Slope	SD	Intercept	SD		
300–150,000	0.9982	1.1203E-10	3.9606E-11	2.0100E-04	1.2202E-04	3.9073E-03	3.3352E-03	81.2	0.03
150–75,000	0.9987	1.5737E-11	2.2915E-11	5.0400E-05	3.5070E-05	4.9600E-04	6.0576E-04	67.9	-0.47

IS: internal standard; SD: standard deviation.

Table 4.3. Summary of accuracy and precision

Compound	Concentration (ng/mL)	Intra-assay		Inter-assay	
		Accuracy (%)	CV (%)	Accuracy (%)	CV (%)
Piperacillin	300	111.83	6.46	109.50	7.32
	900	96.32	7.08	96.41	7.67
	60,000	103.35	4.70	101.85	6.05
	120,000	102.59	4.31	101.30	6.61
Mean		103.52	5.63	102.27	6.91
Tazobactam	150	107.63	8.58	105.30	10.33
	450	97.89	9.65	103.58	8.67
	60,000	100.55	4.45	101.96	5.43
Mean		102.02	7.56	103.61	8.14

CV: coefficient of variation.

Table 4.4. Validation of piperacillin partial dilutions

Piperacillin	Dilution	Conc.	Conc.	Conc.
		1:1	1:3	1:9
Sample #	1	161000	87600	29800
	2	159000	78500	31800
	3	156000	84800	32600
	Theoretical conc.	150000	75000	30000
	mean	158667	83633	31400
	SD	2516.6	4660.8	1442.2
	% CV	1.6	5.6	4.6
	% Dev	5.8	11.5	4.7
	n	3	3	3

Conc: concentration; CV: coefficient of variation; Dev: deviation; SD: standard deviation.

Table 4.5. DBS and plasma concentrations for piperacillin and tazobactam

Piperacillin					
Plasma concentration (mg/L)	N	DBS concentration (mg/L)	Plasma concentration (mg/L)	DBS/Plasma ratio	Hct
<50	7	12.3 (3.3, 46.5)	26.4 (12.5, 36.6)	0.61 (0.31, 3.01)	0.40 (0.32, 0.51)
50–150	21	46.4 (18.4, 97.0)	104.0 (55.7, 150.0)	0.38 (0.25, 1.00)	0.44 (0.30, 0.54)
>150	9	70.2 (49.2, 105.0)	220.0 (154.0, 280.0)	0.35 (0.20, 0.59)	0.43 (0.32, 0.47)
All	37	49.0 (3.3, 105.0)	107.0 (10.5, 280.0)	0.37 (0.20, 3.01)	0.42 (0.30, 0.54)
Tazobactam					
<5	7	2.1 (0.3, 3.4)	4.1 (1.1, 4.9)	0.48 (0.25, 0.84)	0.41 (0.32, 0.51)
5–15	16	5.5 (1.9, 13.3)	10.2 (5.3, 14.5)	0.54 (0.28, 1.09)	0.41 (0.30, 0.54)
>15	14	8.7 (3.3, 14.7)	20.2 (15.2, 28.6)	0.45 (0.22, 0.64)	0.44 (0.32, 0.50)
All	37	5.8 (0.28, 14.7)	12.2 (1.12, 28.6)	0.50 (0.21, 1.41)	0.42 (0.30, 0.54)

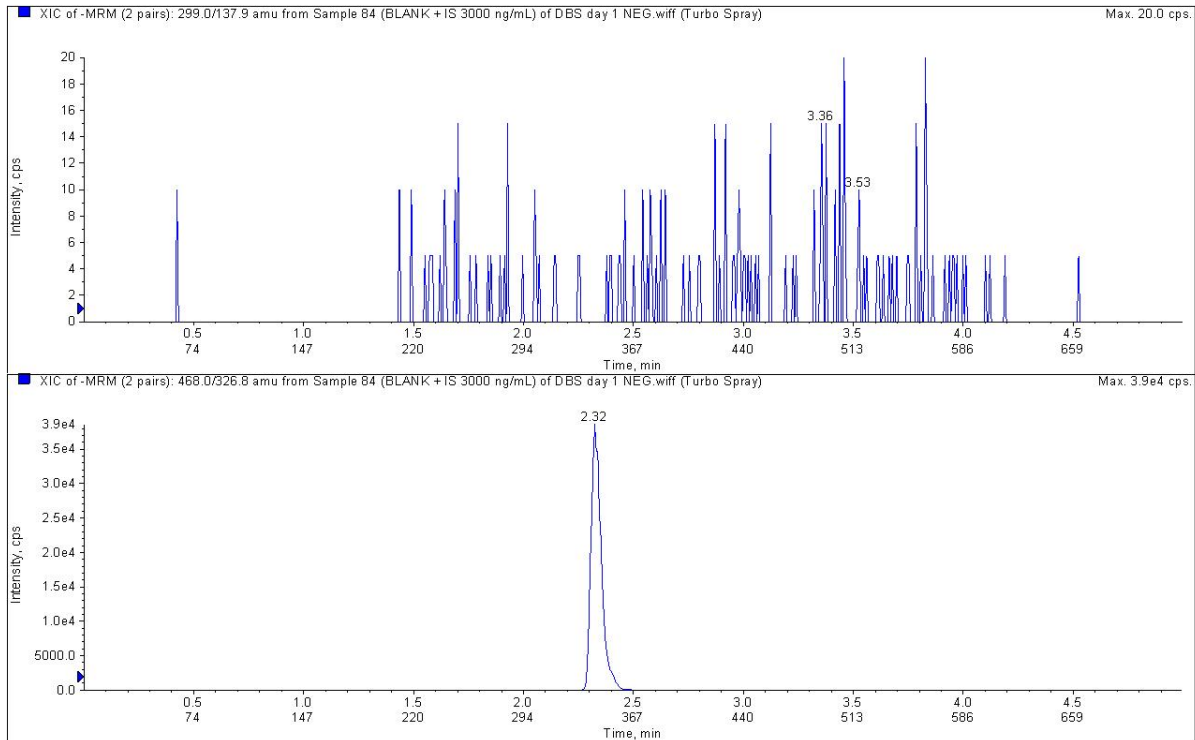
Data are median (range).

DBS: dried blood spot; Hct: hematocrit.



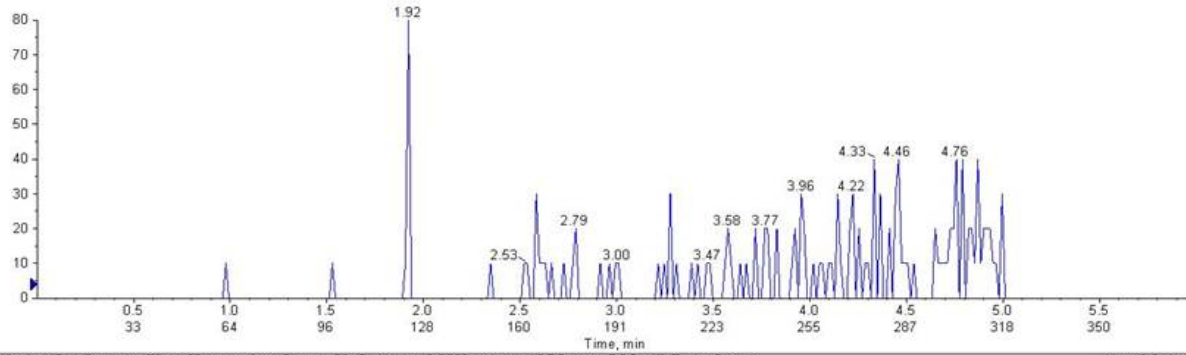
Fig. 4.1. Blank plasma sample run in a) negative (tazobactam top; dicloxacillin [IS] bottom) and b) positive (piperacillin top; dicloxacillin [IS] bottom) ionization mode. IS: internal standard.

A.



B.

XIC of +MRM (9 pairs): 518.2/143.3 amu from Sample 58 (BLANK + IS 3000 ng/mL) of DBS day1 POS.wiff (Turbo Spray) Max. 80.0 c



XIC of +MRM (9 pairs): 470.1/160.1 amu from Sample 58 (BLANK + IS 3000 ng/mL) of DBS day1 POS.wiff (Turbo Spray) Max. 2.3e4 c

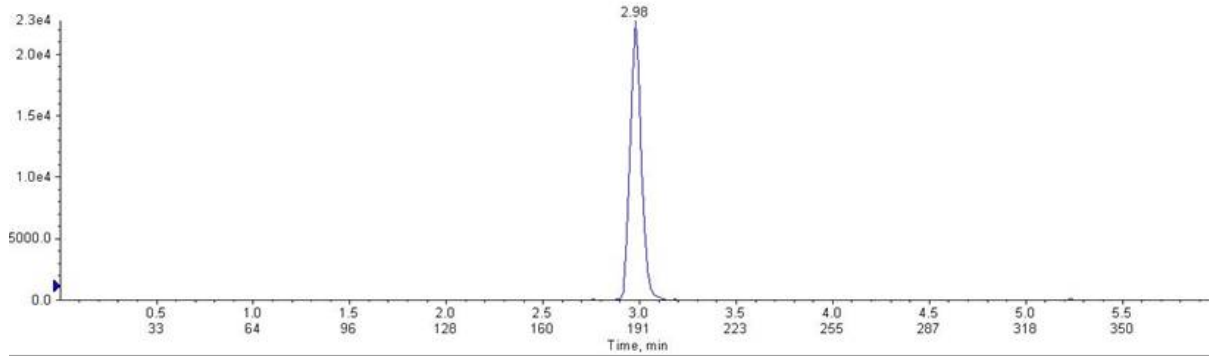
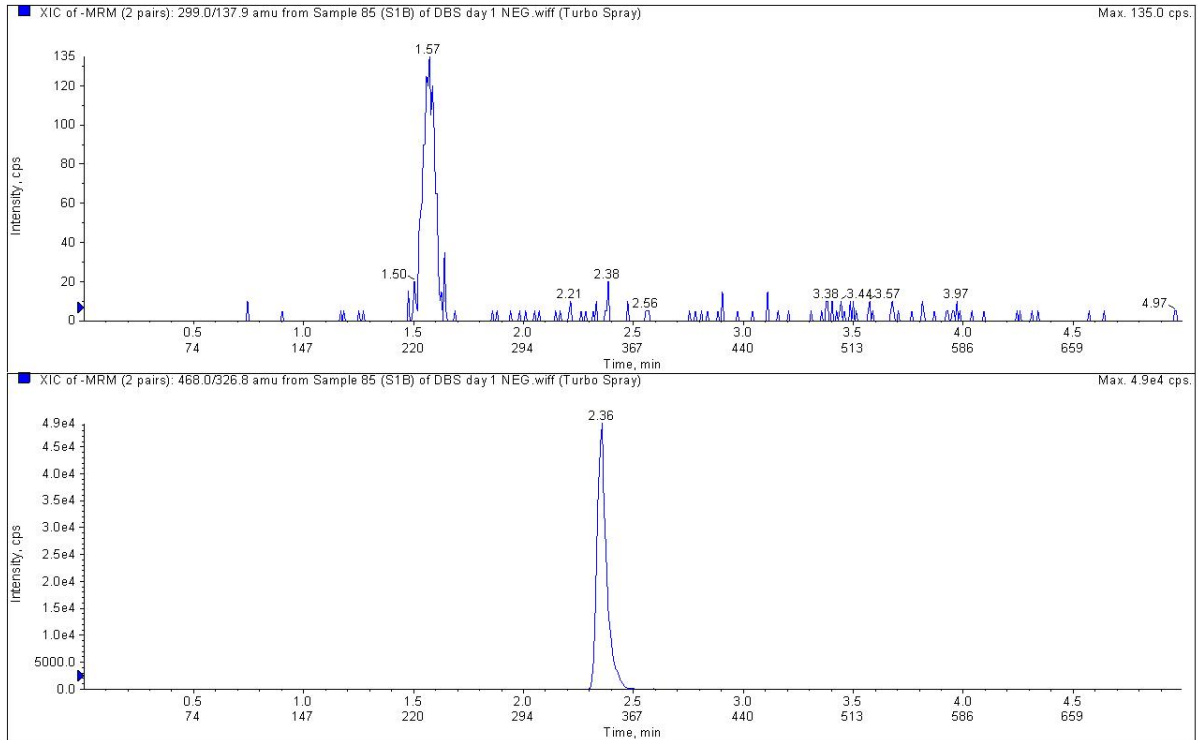
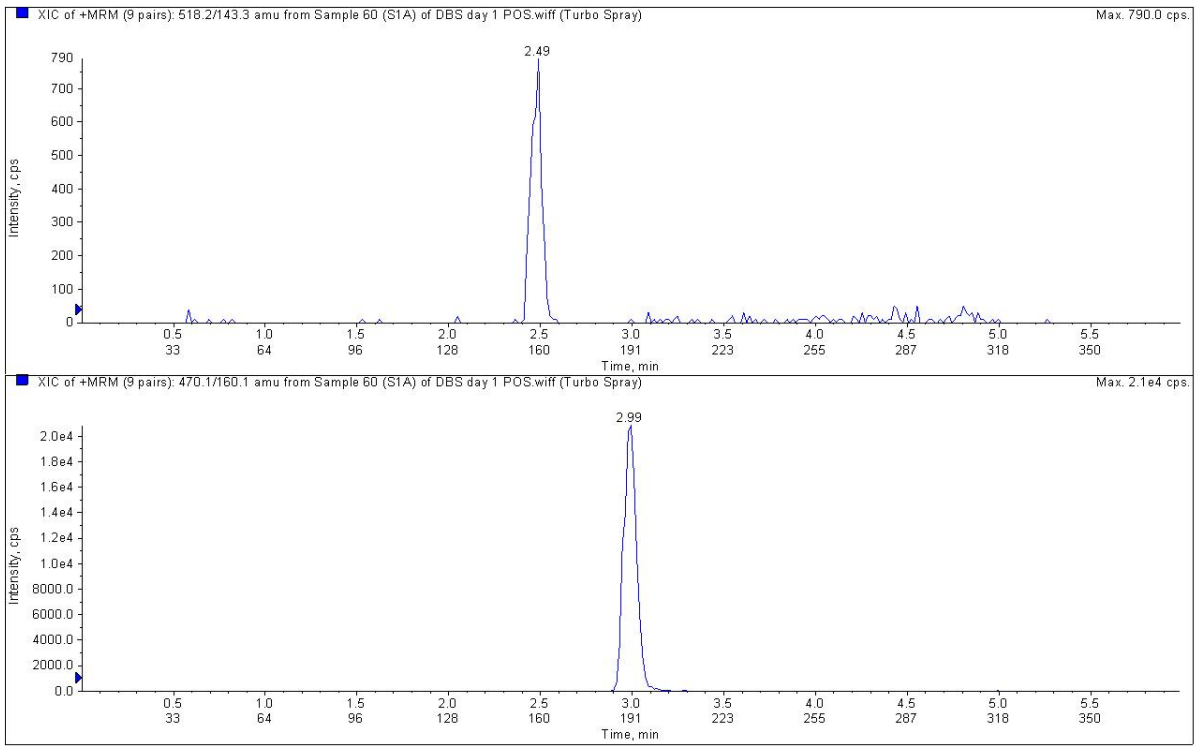


Fig. 4.2. Lower limit of quantification in a) negative (top to bottom: tazobactam and dicloxacillin [IS]) and b) positive (top to bottom: dicloxacillin [IS], piperacillin) ionization mode. Upper limit of quantification in c) negative (top to bottom: tazobactam and dicloxacillin [IS]) and d) positive (top to bottom: dicloxacillin [IS], piperacillin) ionization mode. IS: internal standard.

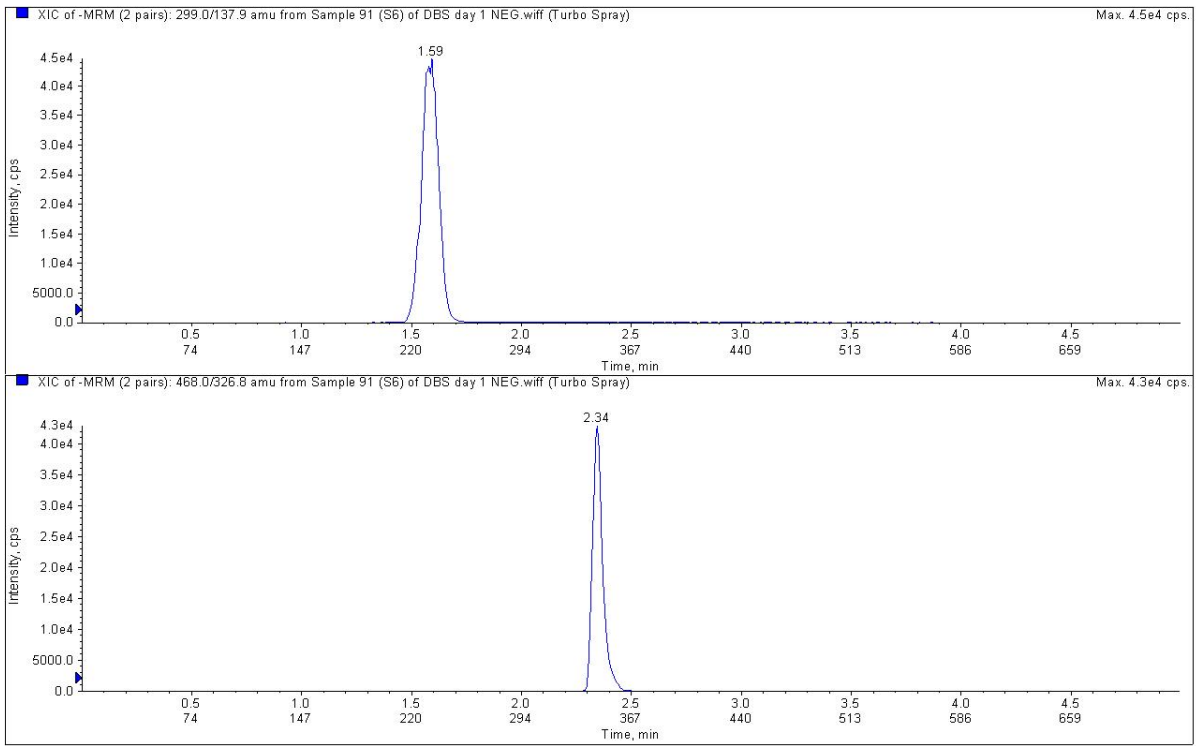
A.



B.



C.



D.

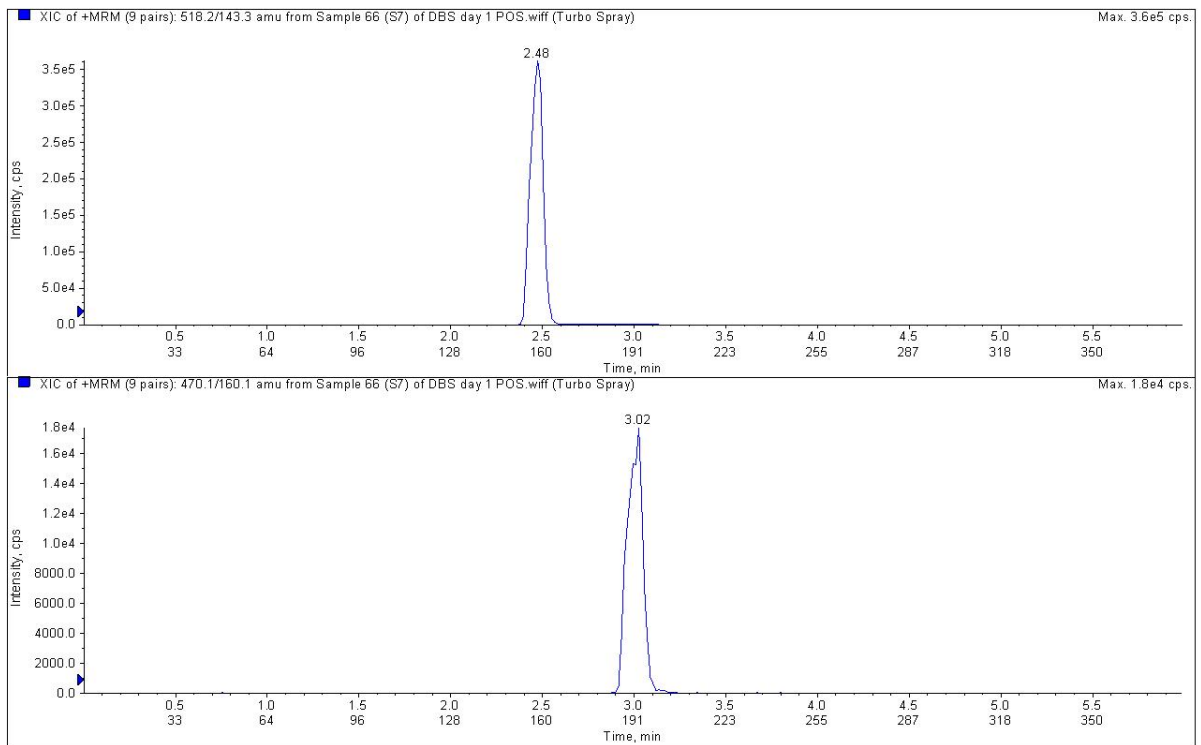


Fig 4.3. On-card stability for piperacillin (gray line) and tazobactam (black line).

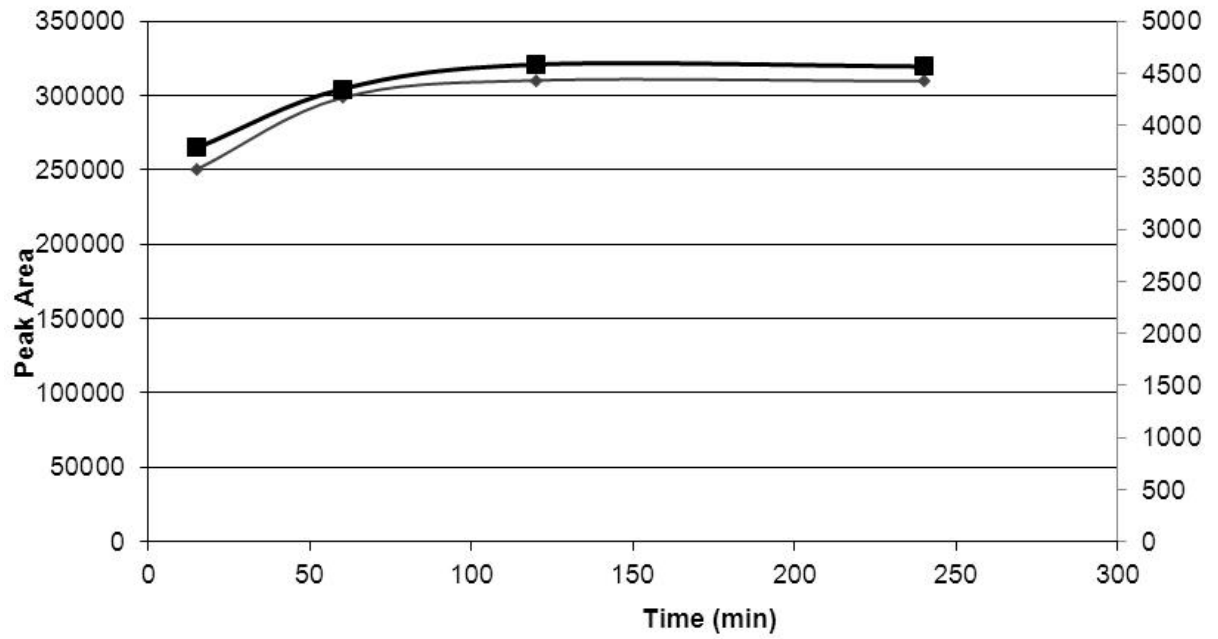
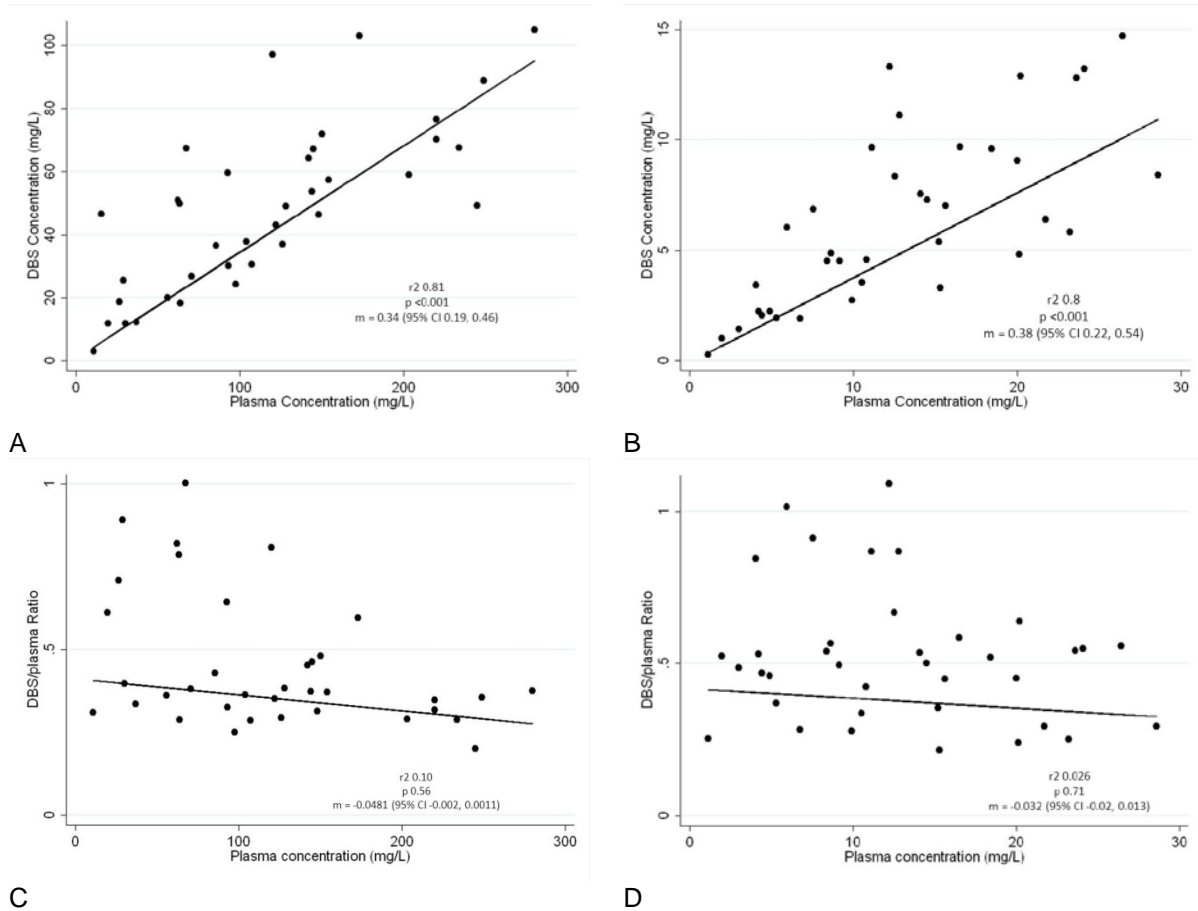


Fig. 4.4. Scatter plots of DBS vs. plasma concentrations for a) piperacillin and b) tazobactam. Scatter plots of DBS-to-plasma concentration ratio vs. plasma concentrations for c) piperacillin and d) tazobactam. DBS: dried blood spot; m: slope. Non-valid samples (N=11) are excluded from all panels. One outlier was excluded from panel C (DBS-to-plasma ratio = 3). Solid line represents the weighted linear regression fit.





## SUMMARY AND FUTURE DIRECTIONS

The studies included in this proposal evaluated the use of several novel, minimal-risk methods to assess the pharmacokinetics (PK) of antimicrobial agents in preterm infants. Such minimal-risk methods seek to address the challenges associated with traditional PK study designs in preterm infants, which have led to profound knowledge gaps about the antimicrobials used most commonly in this vulnerable population. Although the use of minimal-risk methods is an attractive strategy for evaluating the PK of drugs in this context, they have not been systematically validated across antimicrobial classes, and few studies have actually implemented these methods with success.<sup>1,2</sup> The utility of minimal-risk methods may be drug-dependent as they rely on physicochemical properties of the drug. Therefore, the primary goal of this proposal was to evaluate minimal-risk methods using 2 commonly used antimicrobials with different physicochemical properties. The following methods were assessed: the use of scavenged plasma samples to determine the PK of piperacillin and metronidazole; the development of a multiplex assay using ultra-low blood volumes; and the utility of dried blood spot (DBS) sampling.

Scavenged sampling was a successful minimal-risk approach for the development of population PK models, as well as for covariate screening for both piperacillin and metronidazole. A 1-compartment model appropriately described the PK of both drugs and is consistent with prior findings in older children and adults.<sup>1,3-7</sup> In addition, serum creatinine and postmenstrual age were identified as significant covariates explaining the inter-individual

variability in piperacillin and metronidazole clearance, respectively. These findings are also consistent with prior reports and suggest that those covariates could be used to design or refine existing dosing regimens for this population. Collectively, these are important findings because scavenging allowed for development of PK models and covariate relationships using samples that otherwise would have been discarded.

The use of scavenged sampling could have broad applications in preterm infant drug development. Given the low hurdles associated with this sample collection method and the high yield of meaningful PK relationships, this strategy should be strongly considered for initial PK model development of drugs in preterm infants prior to design and implementation of traditional PK studies. As demonstrated for piperacillin and metronidazole, applying scavenged sampling can lead to identification of appropriate structural PK models and critical PK sampling times, as well as key covariates that could be further refined in follow-up traditional PK studies. This strategy will eliminate the “blinded” approach in which traditional PK trials are designed without any prior PK information. Obtaining scavenged sampling PK information prior to conducting traditional PK studies will also lead to a higher probability of trial success as it would allow for a more informed and targeted data collection.

Scavenging of PK samples also proved successful in estimating the bias in metronidazole drug concentrations introduced by this methodology relative to scheduled blood draws. On average, metronidazole concentrations in scavenged samples were 30% lower than those in scheduled blood draws. In addition, residual variability in scavenged samples was higher than that associated with blood draws. The latter finding is expected given errors associated with retrospective data collection of dosing and sampling times of

scavenged samples that contribute to increased variability. Bias introduced by piperacillin scavenged samples was not assessed due to the lack of scheduled blood draws for comparison.

The scavenging approach could also be used to provide definitive dosing recommendations for preterm infants; however, based on the piperacillin and metronidazole experiences, this application is dependent on the drug being studied and the quality of the data collected. During the PK analysis of piperacillin, an important amount of information (from about 20 subjects) could not be used in the analysis due to uncertain documentation of dosing and sampling times, potential sample contamination, or samples collected during drug infusion or intravascular line flush. In addition, after exclusion of these data, PK and variability parameter estimates were unexpected and not consistent with the limited piperacillin PK information in preterm infants. Estimates of clearance and volume of distribution were several-fold higher when compared with published reports.<sup>5,6</sup> These estimates were also physiologically unreliable. It is plausible that piperacillin degradation in scavenged samples was the primary factor influencing the biased PK point estimates. The temperature instability of piperacillin is limited to <4–6 hours,<sup>8</sup> and scavenged samples could have remained at room temperature or in the refrigerator for 48–72 hours prior to freezing. As mentioned, lack of scheduled piperacillin blood draws limited the ability to counterbalance the bias introduced by scavenged samples in the piperacillin analysis.

In contrast, even though most (90%) metronidazole PK samples were scavenged, PK and variability point estimates were consistent and physiologically meaningful. This is likely due to the excellent temperature stability of metronidazole (unlike that of piperacillin).<sup>9</sup> Therefore, scavenged samples not only provided information regarding the structure of the

PK model and influencing covariates, but it also allowed for development of metronidazole dosing recommendations for preterm infants. Moreover, it facilitated the development of a new, simplified scheme based on postmenstrual age that compared very favorably with current dosing guidelines. For this drug, the scavenged sampling approach was a more powerful tool to advance drug development in preterm infants.

The piperacillin and metronidazole experiences using scavenged samples uncovered some advantages and disadvantages of this minimal-risk approach. Advantages included enrollment of infants across a wide range of gestational ages to appropriately explore covariate associations with PK parameters; collection of about 3 samples per subject; minimal demographic data collection to increase study feasibility; collection of clinical data of special interest (i.e., serum creatinine) targeted towards the drugs of interest; and collection of scheduled blood draws in addition to scavenged samples. Some of the limitations of scavenged sampling included uncertainty around dosing and sampling collection dates and times; no documentation of time when samples were frozen; no documentation of concomitant medication; and limited collection of scheduled blood draws. If these limitations are addressed in future trials, scavenged sampling could provide more robust data and widen its application across drugs in preterm infants and older children.

Another minimal-risk method explored in this dissertation was the measurement of piperacillin and tazobactam concentrations in DBS. This sampling technology is of great interest for pediatric pharmacologists given that only 15–30 uL of blood is required for PK sampling. DBS is also advantageous because of the simplicity of sample processing and analysis; however, the application of DBS sampling in infants is limited to 1 clinical trial.<sup>1</sup> A piperacillin and tazobactam multiplex DBS assay involving simple sample preparation was

developed and validated. Piperacillin and tazobactam DBS correlated with paired plasma concentrations; on average, piperacillin and tazobactam DBS concentrations were 50–60% lower than plasma. This finding suggests that piperacillin and tazobactam do not partition into red blood cells, which act as a diluent when DBS (whole blood) concentrations are measured. This should be considered when DBS samples are used as a surrogate for plasma during PK evaluations of piperacillin and tazobactam. This exploratory DBS analysis suggests that DBS can be used to evaluate the PK of piperacillin and tazobactam, but further studies are required.

The minimal-risk methods evaluated in this proposal proved successful in many aspects related to drug development in preterm infants. In the future, prospective trials will need to be conducted to validate these findings. A PK study of piperacillin-tazobactam in preterm infants has been completed. In this study, 32 preterm infants were enrolled and given piperacillin-tazobactam per routine medical care. Scheduled PK blood draws were supplemented with scavenged and DBS samples to validate the bias introduced by these sampling strategies. Data analysis for this trial is ongoing. Similarly, another study of 24 preterm infants will validate the use of scavenged and DBS sampling in subjects treated with metronidazole. These sampling techniques will also supplement scheduled blood draws. In addition to the clinical data of special interest specifically designed for each drug, data regarding time of scavenged sample freezing will also be obtained in these trials. With this information, it will be possible to establish a time cut-off for utilization of scavenged samples for unstable drugs such as piperacillin based on the time needed to freeze the scavenged samples.

In the future, the Pediatric Trials Network will oversee a clinical trial derived from the scavenged sampling experience. The NIH-sponsored Pediatric Opportunistic PK Study (POPS) will be conducted in 15 sites across the United States. PK samples will be obtained from subjects receiving drugs per routine medical care. The study will include children <21 years of age and will address an array of drugs selected through the NIH Best Pharmaceuticals for Children Act (BPCA) prioritization initiative. The lessons learned through the studies evaluated in this dissertation were incorporated into the design of the POPS study, which will begin enrollment by the end of 2011. Another initiative to validate the use of alternative biological sample collection techniques is in process. The DBS technology will be expanded to other body fluids (i.e., dried matrix spots, dried urine spots) to evaluate the PK of anti-staphylococcal antibiotics in children. The study design and funding sources are being assembled for this project.

In summary, minimal-risk methods can revolutionize the way drug development is conducted in preterm infants and can be extrapolated to older pediatric populations. Clearly defined objectives for minimal-risk methods are important to achieve the appropriate balance between study feasibility and data quality. In the future, validation of minimal-risk methods will provide additional evidence of the utility of these approaches. Minimal-risk methods can be applied to other commonly used therapeutics in children to decrease the profound knowledge gap regarding this population.

Appendix 1: Metronidazole Final Model Control File and Output

```
Mon 09/12/2011
12:00 PM
$PROBLEM METRO PPK PREMATURE INFANTS - PPRU SCAVENGE SAMPLING
$INPUT ORDN ID DATE=DROP TIME EVID AMT DUR RATE DI DV SCAV PNA PMA BW CWT SEX RACE HISP
APGAR SRCR2 CWTCL CR
$DATA metf.CSV IGNORE=#
$SUBROUTINES ADVAN1 TRANS2
$PK
IF (AMT.GT.0) THEN
TDOS=TIME
TAD=0.0
ENDIF
IF (AMT.EQ.0) TAD=TIME-TDOS
TVCL=THETA(1)*(CWT/1.5)*((PMA/32)**THETA(3))
CL=TVCL*EXP(ETA(1))
TVV=THETA(2)*(CWT/1.5)
V=TVV
K=CL/V
HFLF=0.693/K
CLKG=CL/CWT
S1=V
$ERROR
IPRED=F
```

```

Y1=F+F*ERR(1)
Y2=F*THETA(4)+F*THETA(4)*ERR(2)
Y=(Y2*SCAV)+(Y1*(1-SCAV))

IRES=DV-F
IWRES=IRES/IPRED
W=F

$THETA
(0.0005, 0.05, 10) ;POP CL CL=L/h, initial estimates from METRO DBS paper
(0.015, 1.5, 10) ;POPV, V=L, 0.7 L/kg from lit
(0.01, 1, 5) ;PMA exponent CL
(0.01, 0.8, 3) ;SCAV bias

$OMEGA
(0.25) ;ETA CL

$$SIGMA
(0.09) ;RV PROPORTIONAL ASSUMING 30%CV
(0.09) ;RV SCAV ASSUMING 30%CV
;QL 0.05 mg/L

$ESTIMATION MAXEVAL=9999 PRINT=5 SIGDIG=3 METHOD=1 INTERACTION NOABORT POSTHOC

$COV PRINT=E

$TABLE ORDN ID TIME TAD CWT AMT CL V K HFLF PMA GA GAGR PNA ETA1 DI IPRED IRES NOPRINT ONEHEADER
FILE=22c.tbl
;$TABLE ID ETA1 TIME IPRED WRES IWRES EVID NOPRINT ONEHEADER FILE=sdtab15c
;$TABLE ID CL CLKG V NOPRINT ONEHEADER FILE=patab15c
;$TABLE ID RACE SEX HISP NOPRINT ONEHEADER FILE=catab22c
;$TABLE ID GA PNA PMA CWT CWTC SRCR2 NOPRINT ONEHEADER FILE=cotab15c

NM-TRAN MESSAGES

```



WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1

(WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.  
CREATING MUMODEL ROUTINE...

FSUBS

FSUBS\_MU.F90

1 file(s) copied.

License Registered to: Duke Clinical Research Institute

Expiration Date: 14 MAR 2012

Current Date: 12 SEP 2011

Days until program expires : 187

1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.1.0  
ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, 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

METRO PPK PREMATURE INFANTS - PPRU SCAVENGE SAMPLING

0DATA CHECKOUT RUN: NO

DATA SET LOCATED ON UNIT NO.: 2

THIS UNIT TO BE REWOUND: NO

NO. OF DATA RECS IN DATA SET: 526

NO. OF DATA ITEMS IN DATA SET: 24

ID DATA ITEM IS DATA ITEM NO.: 2

DEP VARIABLE IS DATA ITEM NO.: 9

MDV DATA ITEM IS DATA ITEM NO.: 24

0INDICES PASSED TO SUBROUTINE PRED:

4 3 5 7 0 0 0 0

0 0

0LABELS FOR DATA ITEMS:

ORDN ID TIME EVID AMT DUR RATE DI DV SCAV GA GAGR PNA PMA BW CWT SEX RACE HISP APGAR SRCR2 CWTC CR  
MDV

0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:

TAD CL V K HFLF IPRE IRES  
0FORMAT FOR DATA:  
(3(6E12.0),5E12.0,1F2.0)

TOT. NO. OF OBS RECS: 116  
TOT. NO. OF INDIVIDUALS: 32  
LENGTH OF THETA: 4  
0DEFAULT THETA BOUNDARY TEST OMITTED: NO  
0OMEGA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1  
0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO  
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 2  
0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO  
0INITIAL ESTIMATE OF THETA:  
LOWER BOUND INITIAL EST UPPER BOUND  
0.5000E-03 0.5000E-01 0.1000E+02  
0.1500E-01 0.1500E+01 0.1000E+02  
0.1000E-01 0.1000E+01 0.5000E+01  
0.1000E-01 0.8000E+00 0.3000E+01  
0INITIAL ESTIMATE OF OMEGA:  
0.2500E+00  
0INITIAL ESTIMATE OF SIGMA:  
0.9000E-01  
0.0000E+00 0.9000E-01  
0ESTIMATION STEP OMITTED: NO  
CONDITIONAL ESTIMATES USED: YES  
CENTERED ETA: NO  
EPS-ETA INTERACTION: YES  
LAPLACIAN OBJ. FUNC.: NO  
NO. OF FUNCT. EVALS. ALLOWED: 9999  
NO. OF SIG. FIGURES REQUIRED: 3  
INTERMEDIATE PRINTOUT: YES  
ESTIMATE OUTPUT TO MSF: NO  
ABORT WITH PRED EXIT CODE 1: NO  
IND. OBJ. FUNC. VALUES SORTED: NO  
0COVARIANCE STEP OMITTED: NO

EIGENVLS. PRINTED: YES  
 SPECIAL COMPUTATION: NO  
 COMPRESSED FORMAT: NO  
 0 TABLES STEP OMITTED: NO  
 NO. OF TABLES: 1  
 0-- TABLE 1 --  
 PRINTED: NO  
 HEADER: YES  
 FILE TO BE FORWARDED: NO  
 0 USER-CHOSEN ITEMS:  
 ORDN ID TIME TAD CWT AMT CL V K HFLF PMA GA GAGR PNA ETA1 DI IPRED IRES

THE FOLLOWING LABELS ARE EQUIVALENT

PRED=PREDI  
 RES=RESI  
 WRES=WRESI  
 1 DOUBLE PRECISION PREDPP VERSION 7.1.0

ONE COMPARTMENT MODEL (ADVAN1)  
 0 MAXIMUM NO. OF BASIC PK PARAMETERS: 2  
 0 BASIC PK PARAMETERS (AFTER TRANSLATION):  
 ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1

TRANSLATOR WILL CONVERT PARAMETERS  
 CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)  
 0 COMPARTMENT ATTRIBUTES  
 COMPT. NO. FUNCTION INITIAL ON/OFF DOSE DEFAULT  
 STATUS ALLOWED FOR DOSE FOR OBS.  
 1 CENTRAL ON NO YES YES YES  
 2 OUTPUT OFF YES NO NO NO

1 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG  
 COMPT. NO. INDICES  
 SCALE BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB  
 FRACTION RATE DURATION LAG

```

1      3      *      *      *      *
2      *      -      -      -      -
- 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.: 4
TIME DATA ITEM IS DATA ITEM NO.: 3
DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 5
DOSE RATE DATA ITEM IS DATA ITEM NO.: 7

```

```

OPK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
1

```

```

#METH: First Order Conditional Estimation with Interaction
MONITORING OF SEARCH:

```

```

0ITERATION NO.: 0 OBJECTIVE VALUE: 495.535088533525 NO. OF FUNC. EVALS.: 8
CUMULATIVE NO. OF FUNC. EVALS.: 8
PARAMETER: 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01
GRADIENT: 2.0918E+01 5.3564E+01 -4.5728E+00 -5.3576E+01 -4.7616E+00 1.2300E+01 -1.3000E+01
0ITERATION NO.: 5 OBJECTIVE VALUE: 481.202580703595 NO. OF FUNC. EVALS.: 9
CUMULATIVE NO. OF FUNC. EVALS.: 53
PARAMETER: -1.5512E-01 -3.8406E-01 6.1768E-01 -1.2882E-01 -1.2671E-01 -9.8676E-01 -2.2379E-02
GRADIENT: -5.5109E+00 -2.8538E+00 -5.7496E+00 3.5143E-01 -1.0822E+01 -1.2520E+01 -2.8998E+01
0ITERATION NO.: 10 OBJECTIVE VALUE: 475.260304388764 NO. OF FUNC. EVALS.: 9
CUMULATIVE NO. OF FUNC. EVALS.: 100
PARAMETER: -1.4965E-01 -3.0776E-01 1.4640E+00 -7.9347E-02 -7.2058E-02 -6.9283E-01 7.8835E-02
GRADIENT: -4.6259E-01 -2.1452E-01 -8.4669E-02 -4.4445E-01 -6.6456E-01 2.0222E-01 3.6555E+00
0ITERATION NO.: 15 OBJECTIVE VALUE: 475.216171934987 NO. OF FUNC. EVALS.: 15
CUMULATIVE NO. OF FUNC. EVALS.: 161
PARAMETER: -1.3444E-01 -2.8783E-01 1.4808E+00 -5.5116E-02 -6.1703E-02 -7.0105E-01 6.5415E-02

```

GRADIENT: 2.4646E-03 -4.6347E-03 1.1323E-03 8.1129E-04 3.5398E-03 -4.5325E-03 1.0535E-03  
ITERATION NO.: 16 OBJECTIVE VALUE: 475.216171934987 NO. OF FUNC. EVALS.:12  
CUMULATIVE NO. OF FUNC. EVALS.: 173  
PARAMETER: -1.3444E-01 -2.8783E-01 1.4808E+00 -5.5116E-02 -6.1703E-02 -7.0105E-01 6.5415E-02  
GRADIENT: 2.4646E-03 -4.6347E-03 1.1323E-03 8.1129E-04 3.5398E-03 -4.5325E-03 1.0535E-03  
Elapsed estimation time in seconds: 1.77

#TERM:  
MINIMIZATION SUCCESSFUL  
NO. OF FUNCTION EVALUATIONS USED: 173  
NO. OF SIG. DIGITS IN FINAL EST.: 3.6

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: 8.1771E-03  
SE: 6.8174E-02

P VAL.: 9.0453E-01

ETAshrink(%): 7.8817E+00  
EPSshrink(%): 1.4778E+01 9.3970E+00

#TERE:  
Elapsed covariance time in seconds: 2.44

1

## Appendix 2: Metronidazole PK Dataset

TABLE NO. 1

ORDN	ID	TIME	TAD	CWT	AMT	CL	V	K	HFLF	PMA	GA	GAGR	PNA	ETA1	DI	IPRED	IRES	DV	PRED	RES	WRES
1.00	41.00	0.00	0.00	1.23	6.70	0.02	0.88	0.02	31.15	33.14	32.00	2.00	8.00	-0.60	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.00	41.00	24.00	0.00	1.23	6.70	0.02	0.88	0.02	30.82	33.29	32.00	2.00	9.00	-0.60	24.00	4.49	-4.49	0.00	2.92	0.00	0.00
3.00	41.00	48.00	0.00	1.23	6.70	0.02	0.88	0.02	30.50	33.43	32.00	2.00	10.00	-0.60	24.00	7.07	-7.07	0.00	3.97	0.00	0.00
4.00	41.00	72.00	0.00	1.23	6.70	0.02	0.88	0.02	30.17	33.57	32.00	2.00	11.00	-0.60	24.00	8.51	-8.51	0.00	4.32	0.00	0.00
5.00	41.00	96.00	0.00	1.23	6.70	0.02	0.88	0.02	29.86	33.71	32.00	2.00	12.00	-0.60	24.00	9.29	-9.29	0.00	4.40	0.00	0.00
6.00	41.00	120.00	0.00	1.23	6.70	0.02	0.88	0.02	29.55	33.86	32.00	2.00	13.00	-0.60	24.00	9.68	-9.68	0.00	4.39	0.00	0.00
7.00	41.00	144.47	0.00	1.23	6.70	0.02	0.88	0.02	29.24	34.00	32.00	2.00	14.00	-0.60	24.47	9.73	-9.73	0.00	4.25	0.00	0.00
8.00	41.00	168.00	0.00	1.23	6.70	0.02	0.88	0.02	28.94	34.14	32.00	2.00	15.00	-0.60	23.53	9.92	-9.92	0.00	4.33	0.00	0.00
9.00	41.00	258.00	0.00	1.23	8.00	0.02	0.88	0.02	27.77	34.71	32.00	2.00	19.00	-0.60	90.00	1.87	-1.87	0.00	0.21	0.00	0.00
10.00	41.00	270.02	0.00	1.23	8.00	0.02	0.88	0.03	27.48	34.86	32.00	2.00	20.00	-0.60	12.02	8.18	-8.18	0.00	5.49	0.00	0.00
11.00	41.00	273.98	3.96	1.23	0.00	0.02	0.88	0.03	27.48	34.86	32.00	2.00	20.00	-0.60	0.00	15.73	-7.68	8.05	8.80	-0.75	-1.06
12.00	41.00	274.00	3.98	1.23	0.00	0.02	0.88	0.03	27.48	34.86	32.00	2.00	20.00	-0.60	0.00	15.72	-3.12	12.60	8.79	3.81	0.70
13.00	41.00	274.25	4.23	1.23	0.00	0.02	0.88	0.03	27.48	34.86	32.00	2.00	20.00	-0.60	0.00	15.62	-2.42	13.20	8.69	4.51	0.97
14.00	41.00	281.97	0.00	1.23	8.00	0.02	0.88	0.03	27.48	34.86	32.00	2.00	20.00	-0.60	11.95	12.86	-12.86	0.00	8.56	0.00	0.00
15.00	41.00	294.00	0.00	1.23	8.00	0.02	0.88	0.03	27.21	35.00	32.00	2.00	21.00	-0.60	12.03	16.24	-16.24	0.00	10.25	0.00	0.00
16.00	41.00	303.25	9.25	1.23	0.00	0.02	0.88	0.03	27.21	35.00	32.00	2.00	21.00	-0.60	0.00	20.11	-3.01	17.10	9.09	8.01	1.25
17.00	41.00	304.25	10.25	1.23	0.00	0.02	0.88	0.03	27.21	35.00	32.00	2.00	21.00	-0.60	0.00	19.60	-1.30	18.30	8.68	9.62	1.86
18.00	42.00	0.00	0.00	1.39	10.00	0.04	0.99	0.04	18.21	31.14	28.00	1.00	17.00	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00
19.00	42.00	12.00	0.00	1.39	10.00	0.04	0.99	0.04	18.21	31.14	28.00	1.00	17.00	0.10	12.00	6.49	-6.49	0.00	6.76	0.00	0.00
20.00	42.00	24.00	0.00	1.39	10.00	0.04	0.99	0.04	18.01	31.29	28.00	1.00	18.00	0.10	12.00	10.55	-10.55	0.00	11.17	0.00	0.00
21.00	42.00	37.40	0.00	1.35	10.00	0.04	0.97	0.04	18.01	31.29	28.00	1.00	18.00	0.10	13.40	12.79	-12.79	0.00	13.79	0.00	0.00
22.00	42.00	41.95	4.55	1.35	0.00	0.04	0.97	0.04	18.01	31.29	28.00	1.00	18.00	0.10	0.00	19.59	-4.19	15.40	14.80	0.60	0.16
23.00	42.00	43.62	6.22	1.35	0.00	0.04	0.97	0.04	18.01	31.29	28.00	1.00	18.00	0.10	0.00	18.38	-3.67	14.70	13.96	0.74	0.20
24.00	42.00	48.73	0.00	1.35	10.00	0.04	0.97	0.04	17.81	31.43	28.00	1.00	19.00	0.10	11.33	15.06	-15.06	0.00	16.34	0.00	0.00
25.00	42.00	60.00	0.00	1.35	10.00	0.04	0.97	0.04	17.81	31.43	28.00	1.00	19.00	0.10	11.27	16.52	-16.52	0.00	18.04	0.00	0.00
26.00	42.00	72.00	0.00	1.35	10.00	0.04	0.97	0.04	17.61	31.57	28.00	1.00	20.00	0.10	12.00	16.89	-16.89	0.00	18.61	0.00	0.00
27.00	42.00	74.73	2.73	1.36	0.00	0.04	0.97	0.04	17.61	31.57	28.00	1.00	20.00	0.10	0.00	24.47	-5.79	18.68	18.71	-0.03	0.02
28.00	42.00	84.72	0.00	1.36	10.00	0.04	0.97	0.04	17.61	31.57	28.00	1.00	20.00	0.10	12.72	16.51	-16.51	0.00	18.36	0.00	0.00

29.00	42.00	96.00	0.00	1.36	10.00	0.04	0.97	0.04	17.41	31.71	28.00	1.00	21.00	0.10	11.28	17.23	-17.23	0.00	19.17	0.00	0.00
30.00	42.00	97.52	1.52	1.36	0.00	0.04	0.97	0.04	17.41	31.71	28.00	1.00	21.00	0.10	0.00	26.09	-8.19	17.90	20.00	-2.10	-0.32
31.00	45.00	0.00	0.00	0.76	4.12	0.01	0.54	0.02	28.91	23.57	22.00	0.00	7.00	0.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00
32.00	45.00	49.00	0.00	0.76	4.12	0.01	0.54	0.02	28.05	23.86	22.00	0.00	9.00	0.33	49.00	2.29	-2.29	0.00	3.19	0.00	0.00
33.00	45.00	96.00	0.00	0.76	4.12	0.01	0.54	0.03	27.24	24.14	22.00	0.00	11.00	0.33	47.00	3.01	-3.01	0.00	4.57	0.00	0.00
34.00	45.00	144.00	0.00	0.76	4.12	0.01	0.54	0.03	26.45	24.43	22.00	0.00	13.00	0.33	48.00	3.04	-3.04	0.00	4.93	0.00	0.00
35.00	45.00	192.00	0.00	0.76	4.12	0.01	0.54	0.03	25.70	24.71	22.00	0.00	15.00	0.33	48.00	2.94	-2.94	0.00	4.94	0.00	0.00
36.00	45.00	240.00	0.00	0.76	4.12	0.02	0.54	0.03	24.97	25.00	22.00	0.00	17.00	0.33	48.00	2.80	-2.80	0.00	4.82	0.00	0.00
37.00	45.00	288.00	0.00	0.76	4.12	0.02	0.54	0.03	24.28	25.29	22.00	0.00	19.00	0.33	48.00	2.67	-2.67	0.00	4.64	0.00	0.00
38.00	45.00	298.15	10.15	0.76	0.00	0.02	0.54	0.03	23.94	25.43	22.00	0.00	20.00	0.33	0.00	7.72	-2.32	5.40	7.09	-1.69	-0.42
39.00	45.00	337.33	0.00	0.76	4.80	0.02	0.54	0.03	23.61	25.57	22.00	0.00	21.00	0.33	49.33	2.44	-2.44	0.00	4.34	0.00	0.00
40.00	45.00	346.05	8.72	0.76	0.00	0.02	0.54	0.03	23.29	25.71	22.00	0.00	22.00	0.33	0.00	8.80	-2.71	6.09	7.84	-1.75	-0.42
63.00	46.00	0.00	0.00	3.50	20.00	0.07	2.50	0.03	24.40	40.14	30.00	2.00	71.00	-0.83	12.00	0.00	0.00	0.00	0.00	0.00	0.00
64.00	46.00	12.00	0.00	3.50	20.00	0.07	2.50	0.03	24.19	40.29	30.00	2.00	72.00	-0.83	12.00	5.74	-5.74	0.00	3.76	0.00	0.00
65.00	46.00	24.00	0.00	3.50	20.00	0.07	2.50	0.03	24.19	40.29	30.00	2.00	72.00	-0.83	12.00	9.82	-9.82	0.00	5.47	0.00	0.00
66.00	46.00	36.00	0.00	3.50	20.00	0.07	2.50	0.03	23.98	40.43	30.00	2.00	73.00	-0.83	12.00	12.67	-12.67	0.00	6.21	0.00	0.00
67.00	46.00	48.00	0.00	3.50	20.00	0.07	2.50	0.03	23.98	40.43	30.00	2.00	73.00	-0.83	12.00	14.68	-14.68	0.00	6.54	0.00	0.00
68.00	46.00	60.00	0.00	3.50	20.00	0.07	2.50	0.03	23.77	40.57	30.00	2.00	74.00	-0.83	12.00	16.06	-16.06	0.00	6.65	0.00	0.00
69.00	46.00	72.00	0.00	3.50	20.00	0.07	2.50	0.03	23.77	40.57	30.00	2.00	74.00	-0.83	12.00	17.03	-17.03	0.00	6.69	0.00	0.00
70.00	46.00	118.35	0.00	3.50	49.00	0.07	2.50	0.03	23.36	40.86	30.00	2.00	76.00	-0.83	46.35	6.35	-6.35	0.00	0.64	0.00	0.00
71.00	46.00	137.03	0.00	3.50	24.00	0.07	2.50	0.03	23.15	41.00	30.00	2.00	77.00	-0.83	18.68	14.99	-14.99	0.00	5.81	0.00	0.00
72.00	46.00	196.00	0.00	3.50	25.00	0.08	2.50	0.03	22.76	41.29	30.00	2.00	79.00	-0.83	58.97	4.10	-4.10	0.00	0.26	0.00	0.00
73.00	46.00	202.77	6.77	3.50	0.00	0.08	2.50	0.03	22.56	41.43	30.00	2.00	80.00	-0.83	0.00	11.57	-1.57	10.00	4.70	5.30	1.95
74.00	46.00	208.00	0.00	3.50	25.00	0.08	2.50	0.03	22.56	41.43	30.00	2.00	80.00	-0.83	12.00	9.85	-9.85	0.00	4.56	0.00	0.00
75.00	46.00	216.42	8.42	3.50	0.00	0.08	2.50	0.03	22.56	41.43	30.00	2.00	80.00	-0.83	0.00	15.43	-5.33	10.10	5.88	4.22	-0.24
76.00	46.00	220.00	0.00	3.50	25.00	0.08	2.50	0.03	22.56	41.43	30.00	2.00	80.00	-0.83	12.00	13.83	-13.83	0.00	6.41	0.00	0.00
77.00	46.00	233.03	0.00	3.50	25.00	0.08	2.50	0.03	22.37	41.57	30.00	2.00	81.00	-0.83	13.03	16.01	-16.01	0.00	6.65	0.00	0.00
78.00	46.00	244.00	0.00	3.50	25.00	0.08	2.50	0.03	22.37	41.57	30.00	2.00	81.00	-0.83	10.97	18.61	-18.61	0.00	7.81	0.00	0.00
79.00	46.00	252.00	8.00	3.96	0.00	0.09	2.83	0.03	22.18	41.71	30.00	2.00	82.00	-0.83	0.00	19.79	-0.05	19.74	6.46	13.28	3.33
80.00	46.00	256.00	0.00	3.96	25.00	0.09	2.83	0.03	22.18	41.71	30.00	2.00	82.00	-0.83	12.00	17.47	-17.47	0.00	6.81	0.00	0.00

81.00	46.00	268.00	0.00	3.96	25.00	0.09	2.83	0.03	22.18	41.71	30.00	2.00	82.00	-0.83	12.00	18.17	-18.17	0.00	6.77	0.00	0.00
82.00	46.00	276.00	8.00	3.96	0.00	0.09	2.83	0.03	21.99	41.86	30.00	2.00	83.00	-0.83	0.00	21.09	-5.39	15.70	6.38	9.32	1.28
83.00	48.00	0.00	0.00	1.58	10.80	0.03	1.13	0.03	23.67	31.00	25.00	0.00	42.00	-0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00
84.00	48.00	12.00	0.00	1.58	10.80	0.03	1.13	0.03	23.40	31.14	25.00	0.00	43.00	-0.15	12.00	6.80	-6.80	0.00	6.42	0.00	0.00
85.00	48.00	24.80	0.00	1.58	10.80	0.03	1.13	0.03	23.40	31.14	25.00	0.00	43.00	-0.15	12.80	11.29	-11.29	0.00	10.37	0.00	0.00
86.00	48.00	36.00	0.00	1.58	10.80	0.03	1.13	0.03	23.14	31.29	25.00	0.00	44.00	-0.15	11.20	15.01	-15.01	0.00	13.58	0.00	0.00
87.00	48.00	48.00	0.00	1.58	10.80	0.03	1.13	0.03	23.14	31.29	25.00	0.00	44.00	-0.15	12.00	17.25	-17.25	0.00	15.32	0.00	0.00
88.00	48.00	50.68	2.68	1.58	0.00	0.03	1.13	0.03	23.14	31.29	25.00	0.00	44.00	-0.15	0.00	24.87	-3.86	21.00	16.26	4.74	0.75
89.00	49.00	0.00	0.00	1.41	7.50	0.01	1.01	0.01	49.91	29.14	25.00	0.00	29.00	-0.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00
90.00	49.00	13.98	13.98	1.41	0.00	0.01	1.01	0.01	49.30	29.29	25.00	0.00	30.00	-0.75	0.00	6.15	-1.73	4.42	3.55	0.87	-0.30
91.00	49.00	24.00	0.00	1.41	7.50	0.01	1.01	0.01	49.30	29.29	25.00	0.00	30.00	-0.75	24.00	5.34	-5.34	0.00	3.70	0.00	0.00
92.00	49.00	48.00	0.00	1.41	7.50	0.01	1.01	0.01	48.71	29.43	25.00	0.00	31.00	-0.75	24.00	9.12	-9.12	0.00	5.47	0.00	0.00
93.00	49.00	71.63	0.00	1.34	7.50	0.01	0.96	0.01	48.13	29.57	25.00	0.00	32.00	-0.75	23.63	12.44	-12.44	0.00	6.68	0.00	0.00
94.00	49.00	87.37	15.74	1.34	0.00	0.01	0.96	0.01	47.55	29.71	25.00	0.00	33.00	-0.75	0.00	16.15	-4.15	12.00	6.43	5.57	0.56
95.00	49.00	96.00	0.00	1.34	7.50	0.01	0.96	0.01	47.55	29.71	25.00	0.00	33.00	-0.75	24.37	14.24	-14.24	0.00	6.91	0.00	0.00
96.00	49.00	111.92	15.92	1.34	0.00	0.01	0.96	0.01	46.99	29.86	25.00	0.00	34.00	-0.75	0.00	17.49	0.51	18.00	6.45	11.55	3.27
97.00	54.00	0.00	0.00	0.86	7.00	0.03	0.62	0.05	13.74	31.86	26.00	1.00	40.00	0.32	0.00	0.00	0.00	0.00	0.00	0.00	0.00
98.00	54.00	23.47	23.47	0.86	0.00	0.03	0.62	0.05	13.59	32.00	26.00	1.00	41.00	0.32	0.00	3.53	-1.13	2.40	3.47	-1.07	-0.65
99.00	55.00	0.00	0.00	1.36	21.00	0.04	0.97	0.04	16.67	32.43	31.00	2.00	9.00	0.08	0.00	0.00	0.00	0.00	0.00	0.00	0.00
100.00	55.00	12.65	0.00	1.36	21.00	0.04	0.97	0.04	16.48	32.57	31.00	2.00	10.00	0.08	12.65	12.95	-12.95	0.00	13.50	0.00	0.00
101.00	55.00	16.40	3.75	1.36	0.00	0.04	0.97	0.04	16.48	32.57	31.00	2.00	10.00	0.08	0.00	29.89	-9.69	20.20	21.90	-1.70	-0.21
102.00	55.00	23.87	0.00	1.36	21.00	0.04	0.97	0.04	16.48	32.57	31.00	2.00	10.00	0.08	11.22	21.83	-21.83	0.00	23.01	0.00	0.00
103.00	55.00	36.48	0.00	1.36	21.00	0.04	0.97	0.04	16.31	32.71	31.00	2.00	11.00	0.08	12.62	25.68	-25.68	0.00	27.50	0.00	0.00
104.00	55.00	37.72	1.24	1.36	0.00	0.04	0.97	0.04	16.31	32.71	31.00	2.00	11.00	0.08	0.00	45.27	-21.87	23.40	33.64	-10.24	-0.95
105.00	55.00	50.15	0.00	1.36	21.00	0.04	0.97	0.04	16.31	32.71	31.00	2.00	11.00	0.08	13.67	26.69	-26.69	0.00	29.02	0.00	0.00
106.00	55.00	62.60	0.00	1.36	21.00	0.04	0.97	0.04	16.13	32.86	31.00	2.00	12.00	0.08	12.45	28.55	-28.55	0.00	31.21	0.00	0.00
107.00	55.00	74.05	0.00	1.36	21.00	0.04	0.97	0.04	16.13	32.86	31.00	2.00	12.00	0.08	11.45	30.94	-30.94	0.00	33.86	0.00	0.00
108.00	55.00	86.07	12.02	1.44	0.00	0.04	1.03	0.04	15.96	33.00	31.00	2.00	13.00	0.08	0.00	29.80	-10.10	19.70	23.37	-3.67	-0.32
109.00	55.00	86.40	0.00	1.44	21.00	0.04	1.03	0.04	15.96	33.00	31.00	2.00	13.00	0.08	12.35	29.38	-29.38	0.00	32.34	0.00	0.00
110.00	55.00	98.13	0.00	1.44	21.00	0.04	1.03	0.04	15.96	33.00	31.00	2.00	13.00	0.08	11.73	30.21	-30.21	0.00	33.31	0.00	0.00



111.00	55.00	110.72	0.00	1.44	21.00	0.05	1.03	0.04	15.79	33.14	31.00	2.00	14.00	0.08	12.58	29.42	-29.42	0.00	32.60	0.00	0.00
112.00	55.00	114.53	3.81	1.48	0.00	0.05	1.06	0.04	15.79	33.14	31.00	2.00	14.00	0.08	0.00	41.42	3.68	45.10	44.61	0.49	0.39
122.00	248.00	0.00	0.00	1.18	5.00	0.05	0.84	0.06	12.57	29.86	23.00	0.00	48.00	0.57	24.00	0.00	0.00	0.00	0.00	0.00	0.00
123.00	248.00	24.00	0.00	1.18	5.00	0.05	0.84	0.06	12.42	30.00	23.00	0.00	49.00	0.57	24.00	1.59	-1.59	0.00	2.81	0.00	0.00
124.00	248.00	48.00	0.00	1.18	5.00	0.05	0.84	0.06	12.28	30.14	23.00	0.00	50.00	0.57	24.00	1.97	-1.97	0.00	4.10	0.00	0.00
125.00	248.00	71.83	0.00	1.18	5.00	0.05	0.84	0.06	12.13	30.29	23.00	0.00	51.00	0.57	23.83	2.06	-2.06	0.00	4.68	0.00	0.00
126.00	248.00	96.00	0.00	1.18	5.00	0.05	0.84	0.06	11.99	30.43	23.00	0.00	52.00	0.57	24.17	2.01	-2.01	0.00	4.85	0.00	0.00
127.00	248.00	119.50	0.00	1.18	5.00	0.05	0.84	0.06	11.85	30.57	23.00	0.00	53.00	0.57	23.50	2.04	-2.04	0.00	4.99	0.00	0.00
128.00	248.00	144.00	0.00	1.18	5.00	0.05	0.84	0.06	11.72	30.71	23.00	0.00	54.00	0.57	24.50	1.90	-1.90	0.00	4.85	0.00	0.00
129.00	248.00	168.00	0.00	1.18	5.00	0.05	0.84	0.06	11.58	30.86	23.00	0.00	55.00	0.57	24.00	1.89	-1.89	0.00	4.82	0.00	0.00
130.00	248.00	184.00	16.00	1.18	0.00	0.05	0.84	0.06	11.45	31.00	23.00	0.00	56.00	0.57	0.00	3.02	-1.58	1.44	4.47	-3.03	-0.95
131.00	248.00	192.58	0.00	1.18	5.00	0.05	0.84	0.06	11.45	31.00	23.00	0.00	56.00	0.57	24.58	1.80	-1.80	0.00	4.67	0.00	0.00
132.00	248.00	208.00	15.42	1.21	0.00	0.05	0.87	0.06	11.32	31.14	23.00	0.00	57.00	0.57	0.00	2.98	-1.23	1.75	4.35	-2.60	-0.71
133.00	248.00	215.73	0.00	1.21	5.00	0.05	0.87	0.06	11.32	31.14	23.00	0.00	57.00	0.57	23.15	1.86	-1.86	0.00	4.67	0.00	0.00
134.00	248.00	232.33	16.60	1.27	0.00	0.06	0.91	0.06	11.19	31.29	23.00	0.00	58.00	0.57	0.00	2.65	-0.54	2.11	4.00	-1.89	-0.26
135.00	248.00	239.73	24.00	1.27	0.00	0.06	0.91	0.06	11.19	31.29	23.00	0.00	58.00	0.57	0.00	1.67	-0.36	1.31	3.09	-1.78	-0.25
136.00	248.00	239.92	0.00	1.27	5.00	0.06	0.91	0.06	11.19	31.29	23.00	0.00	58.00	0.57	24.18	1.66	-1.66	0.00	4.30	0.00	0.00
138.00	248.00	264.00	0.00	1.27	5.00	0.06	0.91	0.06	11.07	31.43	23.00	0.00	59.00	0.57	24.08	1.61	-1.61	0.00	4.22	0.00	0.00
139.00	248.00	279.00	15.00	1.27	0.00	0.06	0.91	0.06	10.94	31.57	23.00	0.00	60.00	0.57	0.00	2.80	-0.25	2.55	4.08	-1.53	-0.01
140.00	269.00	0.00	0.00	1.91	13.00	0.04	1.36	0.03	21.85	36.14	27.00	1.00	64.00	-0.46	0.00	0.00	0.00	0.00	0.00	0.00	0.00
141.00	269.00	6.00	0.00	1.91	13.00	0.04	1.36	0.03	21.85	36.14	27.00	1.00	64.00	-0.46	6.00	7.95	-7.95	0.00	7.15	0.00	0.00
142.00	269.00	12.00	0.00	1.91	13.00	0.04	1.36	0.03	21.64	36.29	27.00	1.00	65.00	-0.46	6.00	14.49	-14.49	0.00	12.41	0.00	0.00
143.00	269.00	18.00	0.00	1.91	13.00	0.04	1.36	0.03	21.64	36.29	27.00	1.00	65.00	-0.46	6.00	19.89	-19.89	0.00	16.30	0.00	0.00
144.00	269.00	24.00	0.00	1.91	13.00	0.04	1.36	0.03	21.64	36.29	27.00	1.00	65.00	-0.46	6.00	24.35	-24.35	0.00	19.17	0.00	0.00
145.00	269.00	30.00	0.00	1.91	13.00	0.04	1.36	0.03	21.64	36.29	27.00	1.00	65.00	-0.46	6.00	28.02	-28.02	0.00	21.28	0.00	0.00
146.00	269.00	36.00	0.00	1.91	13.00	0.04	1.36	0.03	21.43	36.43	27.00	1.00	66.00	-0.46	6.00	31.00	-31.00	0.00	22.78	0.00	0.00
147.00	269.00	42.00	0.00	1.91	13.00	0.04	1.36	0.03	21.43	36.43	27.00	1.00	66.00	-0.46	6.00	33.45	-33.45	0.00	23.88	0.00	0.00
148.00	269.00	48.00	0.00	1.91	13.00	0.04	1.36	0.03	21.43	36.43	27.00	1.00	66.00	-0.46	6.00	35.47	-35.47	0.00	24.69	0.00	0.00
149.00	269.00	54.00	0.00	1.91	13.00	0.04	1.36	0.03	21.43	36.43	27.00	1.00	66.00	-0.46	6.00	37.13	-37.13	0.00	25.29	0.00	0.00
150.00	269.00	60.00	0.00	1.91	13.00	0.04	1.36	0.03	21.22	36.57	27.00	1.00	67.00	-0.46	6.00	38.43	-38.43	0.00	25.65	0.00	0.00

151.00	269.00	67.75	0.00	1.91	13.00	0.04	1.36	0.03	21.22	36.57	27.00	1.00	67.00	-0.46	7.75	37.30	-37.30	0.00	23.69	0.00	0.00
152.00	269.00	72.00	0.00	1.91	13.00	0.04	1.36	0.03	21.22	36.57	27.00	1.00	67.00	-0.46	4.25	40.84	-40.84	0.00	26.79	0.00	0.00
153.00	269.00	78.00	0.00	1.91	13.00	0.04	1.36	0.03	21.22	36.57	27.00	1.00	67.00	-0.46	6.00	41.48	-41.48	0.00	26.75	0.00	0.00
154.00	269.00	84.00	0.00	1.91	13.00	0.04	1.36	0.03	21.01	36.71	27.00	1.00	68.00	-0.46	6.00	41.92	-41.92	0.00	26.65	0.00	0.00
155.00	269.00	90.00	0.00	1.91	13.00	0.04	1.36	0.03	21.01	36.71	27.00	1.00	68.00	-0.46	6.00	42.29	-42.29	0.00	26.57	0.00	0.00
156.00	269.00	96.00	0.00	1.91	13.00	0.04	1.36	0.03	21.01	36.71	27.00	1.00	68.00	-0.46	6.00	42.58	-42.58	0.00	26.52	0.00	0.00
157.00	269.00	102.00	0.00	1.91	13.00	0.04	1.36	0.03	21.01	36.71	27.00	1.00	68.00	-0.46	6.00	42.83	-42.83	0.00	26.47	0.00	0.00
158.00	269.00	108.00	0.00	1.91	13.00	0.05	1.36	0.03	20.81	36.86	27.00	1.00	69.00	-0.46	6.00	42.95	-42.95	0.00	26.37	0.00	0.00
159.00	269.00	115.75	0.00	1.91	13.00	0.05	1.36	0.03	20.81	36.86	27.00	1.00	69.00	-0.46	7.75	40.61	-40.61	0.00	23.98	0.00	0.00
160.00	269.00	121.40	0.00	1.91	13.00	0.05	1.36	0.03	20.81	36.86	27.00	1.00	69.00	-0.46	5.65	41.62	-41.62	0.00	25.00	0.00	0.00
161.00	269.00	126.00	0.00	1.91	13.00	0.05	1.36	0.03	20.81	36.86	27.00	1.00	69.00	-0.46	4.60	43.96	-43.96	0.00	27.22	0.00	0.00
162.00	269.00	132.00	0.00	1.91	13.00	0.05	1.36	0.03	20.61	37.00	27.00	1.00	70.00	-0.46	6.00	43.79	-43.79	0.00	26.83	0.00	0.00
163.00	269.00	140.03	0.00	1.91	13.00	0.05	1.36	0.03	20.61	37.00	27.00	1.00	70.00	-0.46	8.03	40.77	-40.77	0.00	23.83	0.00	0.00
164.00	269.00	147.57	0.00	1.91	13.00	0.05	1.36	0.03	20.61	37.00	27.00	1.00	70.00	-0.46	7.53	39.11	-39.11	0.00	22.45	0.00	0.00
165.00	269.00	152.00	0.00	1.91	13.00	0.05	1.36	0.03	20.61	37.00	27.00	1.00	70.00	-0.46	4.43	41.98	-41.98	0.00	25.39	0.00	0.00
166.00	269.00	158.00	0.00	1.91	13.00	0.05	1.36	0.03	20.42	37.14	27.00	1.00	71.00	-0.46	6.00	42.09	-42.09	0.00	25.42	0.00	0.00
167.00	269.00	164.25	0.00	1.91	13.00	0.05	1.36	0.03	20.42	37.14	27.00	1.00	71.00	-0.46	6.25	41.83	-41.83	0.00	25.10	0.00	0.00
168.00	269.00	174.00	0.00	1.91	13.00	0.05	1.36	0.03	20.42	37.14	27.00	1.00	71.00	-0.46	9.75	36.95	-36.95	0.00	20.62	0.00	0.00
169.00	269.00	180.00	0.00	1.91	13.00	0.05	1.36	0.03	20.22	37.29	27.00	1.00	72.00	-0.46	6.00	37.92	-37.92	0.00	21.90	0.00	0.00
170.00	269.00	182.00	2.00	1.91	0.00	0.05	1.36	0.03	20.22	37.29	27.00	1.00	72.00	-0.46	0.00	44.39	-6.09	38.30	20.20	18.10	1.49
171.00	269.00	186.00	0.00	1.91	13.00	0.05	1.36	0.03	20.22	37.29	27.00	1.00	72.00	-0.46	6.00	38.70	-38.70	0.00	22.82	0.00	0.00
172.00	269.00	192.00	0.00	1.91	13.00	0.05	1.36	0.03	20.22	37.29	27.00	1.00	72.00	-0.46	6.00	39.34	-39.34	0.00	23.48	0.00	0.00
173.00	269.00	198.00	0.00	1.91	13.00	0.05	1.36	0.03	20.22	37.29	27.00	1.00	72.00	-0.46	6.00	39.86	-39.86	0.00	23.96	0.00	0.00
174.00	269.00	204.00	0.00	1.91	13.00	0.05	1.36	0.03	20.03	37.43	27.00	1.00	73.00	-0.46	6.00	40.21	-40.21	0.00	24.24	0.00	0.00
175.00	269.00	206.00	2.00	1.91	0.00	0.05	1.36	0.03	20.03	37.43	27.00	1.00	73.00	-0.46	0.00	46.50	-9.50	37.00	21.68	15.32	0.99
176.00	660.00	0.00	0.00	0.85	12.00	0.02	0.61	0.04	19.11	30.57	27.00	1.00	25.00	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00
177.00	660.00	12.00	0.00	0.85	12.00	0.02	0.61	0.04	19.11	30.57	27.00	1.00	25.00	0.09	12.00	13.01	-13.01	0.00	13.50	0.00	0.00
178.00	660.00	24.00	0.00	0.85	12.00	0.02	0.61	0.04	18.89	30.71	27.00	1.00	26.00	0.09	12.00	21.32	-21.32	0.00	22.48	0.00	0.00
179.00	660.00	36.00	0.00	0.85	12.00	0.02	0.61	0.04	18.89	30.71	27.00	1.00	26.00	0.09	12.00	26.67	-26.67	0.00	28.49	0.00	0.00
180.00	660.00	48.00	0.00	0.85	12.00	0.02	0.61	0.04	18.68	30.86	27.00	1.00	27.00	0.09	12.00	29.96	-29.96	0.00	32.38	0.00	0.00

181.00	660.00	60.00	0.00	0.85	12.00	0.02	0.61	0.04	18.68	30.86	27.00	1.00	27.00	0.09	12.00	32.08	-32.08	0.00	34.96	0.00	0.00
182.00	660.00	72.00	0.00	0.85	12.00	0.02	0.61	0.04	18.46	31.00	27.00	1.00	28.00	0.09	12.00	33.26	-33.26	0.00	36.52	0.00	0.00
183.00	660.00	84.00	0.00	0.85	12.00	0.02	0.61	0.04	18.46	31.00	27.00	1.00	28.00	0.09	12.00	34.01	-34.01	0.00	37.55	0.00	0.00
184.00	660.00	96.00	0.00	0.85	12.00	0.02	0.61	0.04	18.25	31.14	27.00	1.00	29.00	0.09	12.00	34.32	-34.32	0.00	38.06	0.00	0.00
185.00	660.00	108.00	0.00	0.85	12.00	0.02	0.61	0.04	18.25	31.14	27.00	1.00	29.00	0.09	12.00	34.51	-34.51	0.00	38.39	0.00	0.00
186.00	660.00	120.00	0.00	0.85	12.00	0.02	0.61	0.04	18.05	31.29	27.00	1.00	30.00	0.09	12.00	34.46	-34.46	0.00	38.43	0.00	0.00
187.00	660.00	132.00	0.00	0.85	12.00	0.02	0.61	0.04	18.05	31.29	27.00	1.00	30.00	0.09	12.00	34.43	-34.43	0.00	38.46	0.00	0.00
188.00	660.00	144.00	0.00	0.85	12.00	0.02	0.61	0.04	17.84	31.43	27.00	1.00	31.00	0.09	12.00	34.23	-34.23	0.00	38.30	0.00	0.00
189.00	660.00	146.00	2.00	0.85	0.00	0.02	0.61	0.04	17.84	31.43	27.00	1.00	31.00	0.09	0.00	50.29	-15.69	34.60	38.79	-4.19	-0.30
190.00	660.00	156.00	0.00	0.85	12.00	0.02	0.61	0.04	17.84	31.43	27.00	1.00	31.00	0.09	12.00	34.10	-34.10	0.00	38.19	0.00	0.00
191.00	660.00	158.25	2.25	0.85	0.00	0.02	0.61	0.04	17.84	31.43	27.00	1.00	31.00	0.09	0.00	49.68	-9.58	40.10	38.38	1.72	0.19
192.00	662.00	0.00	0.00	0.98	14.70	0.01	0.70	0.02	38.67	27.86	27.00	1.00	0.00	-0.38	0.00	0.00	0.00	0.00	0.00	0.00	0.00
193.00	662.00	12.00	0.00	0.98	14.70	0.01	0.70	0.02	38.19	28.00	27.00	1.00	1.00	-0.38	12.00	17.02	-17.02	0.00	15.45	0.00	0.00
194.00	662.00	24.00	0.00	0.98	14.70	0.01	0.70	0.02	38.19	28.00	27.00	1.00	1.00	-0.38	12.00	30.70	-30.70	0.00	26.69	0.00	0.00
195.00	662.00	36.00	0.00	0.98	14.70	0.01	0.70	0.02	37.71	28.14	27.00	1.00	2.00	-0.38	12.00	41.60	-41.60	0.00	34.72	0.00	0.00
196.00	662.00	48.00	0.00	0.98	14.70	0.01	0.70	0.02	37.71	28.14	27.00	1.00	2.00	-0.38	12.00	50.34	-50.34	0.00	40.54	0.00	0.00
197.00	662.00	60.00	0.00	0.98	14.70	0.01	0.70	0.02	37.23	28.29	27.00	1.00	3.00	-0.38	12.00	57.19	-57.19	0.00	44.57	0.00	0.00
198.00	662.00	72.00	0.00	0.98	14.70	0.01	0.70	0.02	37.23	28.29	27.00	1.00	3.00	-0.38	12.00	62.67	-62.67	0.00	47.49	0.00	0.00
199.00	662.00	84.00	0.00	0.98	14.70	0.01	0.70	0.02	36.77	28.43	27.00	1.00	4.00	-0.38	12.00	66.86	-66.86	0.00	49.38	0.00	0.00
200.00	662.00	96.00	0.00	0.98	14.70	0.01	0.70	0.02	36.77	28.43	27.00	1.00	4.00	-0.38	12.00	70.21	-70.21	0.00	50.75	0.00	0.00
201.00	662.00	108.00	0.00	0.98	14.70	0.01	0.70	0.02	36.32	28.57	27.00	1.00	5.00	-0.38	12.00	72.67	-72.67	0.00	51.52	0.00	0.00
202.00	662.00	120.00	0.00	0.98	14.70	0.01	0.70	0.02	36.32	28.57	27.00	1.00	5.00	-0.38	12.00	74.63	-74.63	0.00	52.07	0.00	0.00
203.00	662.00	132.00	0.00	0.98	14.70	0.01	0.70	0.02	35.87	28.71	27.00	1.00	6.00	-0.38	12.00	75.98	-75.98	0.00	52.24	0.00	0.00
204.00	662.00	144.00	0.00	0.98	14.70	0.01	0.70	0.02	35.87	28.71	27.00	1.00	6.00	-0.38	12.00	77.04	-77.04	0.00	52.37	0.00	0.00
205.00	662.00	156.00	0.00	0.98	14.70	0.01	0.70	0.02	35.43	28.86	27.00	1.00	7.00	-0.38	12.00	77.67	-77.67	0.00	52.24	0.00	0.00
206.00	662.00	168.00	0.00	0.98	14.70	0.01	0.70	0.02	35.43	28.86	27.00	1.00	7.00	-0.38	12.00	78.16	-78.16	0.00	52.15	0.00	0.00
207.00	662.00	179.50	11.50	0.98	0.00	0.01	0.70	0.02	35.00	29.00	27.00	1.00	8.00	-0.38	0.00	79.10	-10.60	68.50	37.53	30.97	1.42
208.00	815.00	0.00	0.00	2.54	17.00	0.06	1.82	0.03	22.27	35.29	25.00	0.00	69.00	-0.42	0.00	0.00	0.00	0.00	0.00	0.00	0.00
209.00	815.00	5.78	0.00	2.54	17.00	0.06	1.82	0.03	22.04	35.43	25.00	0.00	70.00	-0.42	5.78	7.93	-7.93	0.00	7.28	0.00	0.00
210.00	815.00	11.40	0.00	2.54	17.00	0.06	1.82	0.03	22.04	35.43	25.00	0.00	70.00	-0.42	5.62	14.62	-14.62	0.00	12.91	0.00	0.00

211.00	815.00	18.62	0.00	2.54	17.00	0.06	1.82	0.03	22.04	35.43	25.00	0.00	70.00	-0.42	7.22	19.24	-19.24	0.00	15.96	0.00	0.00
212.00	815.00	24.53	0.00	2.54	17.00	0.06	1.82	0.03	22.04	35.43	25.00	0.00	70.00	-0.42	5.92	23.88	-23.88	0.00	19.28	0.00	0.00
213.00	815.00	31.22	0.00	2.54	17.00	0.06	1.82	0.03	21.82	35.57	25.00	0.00	71.00	-0.42	6.68	27.00	-27.00	0.00	20.93	0.00	0.00
214.00	815.00	33.63	2.41	2.54	0.00	0.06	1.82	0.03	21.82	35.57	25.00	0.00	71.00	-0.42	0.00	33.83	3.77	37.60	19.38	18.22	2.60
215.00	815.00	37.15	0.00	2.54	17.00	0.06	1.82	0.03	21.82	35.57	25.00	0.00	71.00	-0.42	5.93	30.25	-30.25	0.00	22.95	0.00	0.00
216.00	815.00	42.37	0.00	2.54	17.00	0.06	1.82	0.03	21.82	35.57	25.00	0.00	71.00	-0.42	5.22	33.69	-33.69	0.00	25.31	0.00	0.00
217.00	815.00	47.83	0.00	2.54	17.00	0.06	1.82	0.03	21.82	35.57	25.00	0.00	71.00	-0.42	5.47	36.33	-36.33	0.00	26.84	0.00	0.00
218.00	815.00	53.55	0.00	2.54	17.00	0.06	1.82	0.03	21.82	35.57	25.00	0.00	71.00	-0.42	5.72	38.23	-38.23	0.00	27.67	0.00	0.00
219.00	815.00	58.27	4.72	2.56	0.00	0.06	1.83	0.03	21.61	35.71	25.00	0.00	72.00	-0.42	0.00	40.64	-17.04	23.60	20.93	2.68	-0.32
220.00	820.00	0.00	0.00	1.61	22.00	0.05	1.15	0.04	15.94	33.43	28.00	1.00	38.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00
221.00	820.00	24.00	0.00	1.61	11.00	0.05	1.15	0.04	15.78	33.57	28.00	1.00	39.00	0.05	24.00	6.80	-6.80	0.00	7.17	0.00	0.00
222.00	820.00	59.52	0.00	1.61	11.00	0.05	1.15	0.04	15.45	33.86	28.00	1.00	41.00	0.05	35.52	3.37	-3.37	0.00	3.73	0.00	0.00
223.00	820.00	71.03	0.00	1.61	11.00	0.05	1.15	0.04	15.45	33.86	28.00	1.00	41.00	0.05	11.52	7.84	-7.84	0.00	8.27	0.00	0.00
224.00	820.00	74.82	3.79	1.61	0.00	0.05	1.15	0.04	15.45	33.86	28.00	1.00	41.00	0.05	0.00	14.85	-1.85	13.00	10.94	2.06	0.59
225.00	820.00	83.78	0.00	1.61	11.00	0.05	1.15	0.05	15.29	34.00	28.00	1.00	42.00	0.05	12.75	9.89	-9.89	0.00	10.43	0.00	0.00
226.00	820.00	85.92	2.14	1.59	0.00	0.05	1.14	0.05	15.29	34.00	28.00	1.00	42.00	0.05	0.00	18.07	-3.97	14.10	13.30	0.80	0.17
227.00	820.00	95.98	0.00	1.59	11.00	0.05	1.14	0.05	15.29	34.00	28.00	1.00	42.00	0.05	12.20	11.45	-11.45	0.00	12.10	0.00	0.00
228.00	820.00	108.13	0.00	1.59	11.00	0.05	1.14	0.05	15.13	34.14	28.00	1.00	43.00	0.05	12.15	12.23	-12.23	0.00	12.96	0.00	0.00
229.00	820.00	118.50	10.37	1.61	0.00	0.05	1.15	0.05	15.13	34.14	28.00	1.00	43.00	0.05	0.00	13.59	-4.09	9.50	10.25	-0.75	-0.29
230.00	820.00	120.80	0.00	1.61	11.00	0.05	1.15	0.05	15.13	34.14	28.00	1.00	43.00	0.05	12.67	12.23	-12.23	0.00	13.01	0.00	0.00
231.00	820.00	131.50	0.00	1.61	11.00	0.05	1.15	0.05	14.97	34.29	28.00	1.00	44.00	0.05	10.70	13.41	-13.41	0.00	14.24	0.00	0.00
232.00	820.00	134.25	2.75	1.65	0.00	0.05	1.18	0.05	14.97	34.29	28.00	1.00	44.00	0.05	0.00	19.92	-5.32	14.60	14.80	-0.20	-0.09
261.00	828.00	0.00	0.00	1.41	10.00	0.03	1.01	0.03	20.51	32.43	29.00	1.00	22.00	-0.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00
262.00	828.00	11.35	0.00	1.41	10.00	0.03	1.01	0.03	20.51	32.43	29.00	1.00	22.00	-0.12	11.35	6.87	-6.87	0.00	6.55	0.00	0.00
263.00	828.00	24.33	0.00	1.41	10.00	0.03	1.01	0.03	20.29	32.57	29.00	1.00	23.00	-0.12	12.98	10.88	-10.88	0.00	10.08	0.00	0.00
264.00	828.00	37.05	0.00	1.41	10.00	0.03	1.01	0.03	20.07	32.71	29.00	1.00	24.00	-0.12	12.72	13.52	-13.52	0.00	12.28	0.00	0.00
265.00	828.00	48.85	0.00	1.41	10.00	0.03	1.01	0.03	20.07	32.71	29.00	1.00	24.00	-0.12	11.80	15.70	-15.70	0.00	14.12	0.00	0.00
266.00	828.00	59.65	0.00	1.41	10.00	0.03	1.01	0.03	20.07	32.71	29.00	1.00	24.00	-0.12	10.80	17.76	-17.76	0.00	15.89	0.00	0.00
267.00	828.00	72.23	0.00	1.41	10.00	0.04	1.01	0.03	19.85	32.86	29.00	1.00	25.00	-0.12	12.58	17.95	-17.95	0.00	15.82	0.00	0.00
268.00	828.00	84.15	0.00	1.41	10.00	0.04	1.01	0.03	19.85	32.86	29.00	1.00	25.00	-0.12	11.92	18.49	-18.49	0.00	16.19	0.00	0.00

269.00	828.00	98.30	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.64	33.00	29.00	1.00	26.00	-0.12	14.15	17.35	-17.35	0.00	14.95	0.00	0.00
270.00	828.00	108.27	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.64	33.00	29.00	1.00	26.00	-0.12	9.97	19.30	-19.30	0.00	16.83	0.00	0.00
271.00	828.00	119.85	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.43	33.14	29.00	1.00	27.00	-0.12	11.58	19.45	-19.45	0.00	16.89	0.00	0.00
272.00	828.00	132.67	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.22	33.29	29.00	1.00	28.00	-0.12	12.82	18.61	-18.61	0.00	16.01	0.00	0.00
273.00	828.00	136.77	4.10	1.41	0.00	0.04	1.01	0.04	0.04	19.22	33.29	29.00	1.00	28.00	-0.12	0.00	24.76	-1.66	23.10	15.76	7.34	1.18
274.00	828.00	143.78	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.22	33.29	29.00	1.00	28.00	-0.12	11.12	19.23	-19.23	0.00	16.61	0.00	0.00
275.00	828.00	155.87	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.22	33.29	29.00	1.00	28.00	-0.12	12.08	18.96	-18.96	0.00	16.32	0.00	0.00
276.00	828.00	167.67	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.02	33.43	29.00	1.00	29.00	-0.12	11.80	18.90	-18.90	0.00	16.25	0.00	0.00
277.00	828.00	179.85	0.00	1.41	10.00	0.04	1.01	0.04	0.04	19.02	33.43	29.00	1.00	29.00	-0.12	12.18	18.61	-18.61	0.00	15.96	0.00	0.00
278.00	828.00	191.70	0.00	1.41	10.00	0.04	1.01	0.04	0.04	18.82	33.57	29.00	1.00	30.00	-0.12	11.85	18.55	-18.55	0.00	15.92	0.00	0.00
279.00	828.00	203.62	0.00	1.41	10.00	0.04	1.01	0.04	0.04	18.82	33.57	29.00	1.00	30.00	-0.12	11.92	18.47	-18.47	0.00	15.85	0.00	0.00
280.00	828.00	215.32	0.00	1.41	10.00	0.04	1.01	0.04	0.04	18.62	33.71	29.00	1.00	31.00	-0.12	11.70	18.49	-18.49	0.00	15.87	0.00	0.00
281.00	828.00	227.55	0.00	1.41	10.00	0.04	1.01	0.04	0.04	18.62	33.71	29.00	1.00	31.00	-0.12	12.23	18.13	-18.13	0.00	15.53	0.00	0.00
282.00	828.00	233.43	5.88	1.54	0.00	0.04	1.10	0.04	0.04	18.43	33.86	29.00	1.00	32.00	-0.12	0.00	20.72	-8.62	12.10	13.05	-0.94	-0.59
283.00	831.00	0.00	0.00	0.79	6.00	0.02	0.57	0.03	0.03	20.28	26.14	24.00	0.00	15.00	0.42	0.00	0.00	0.00	0.00	0.00	0.00	0.00
284.00	831.00	22.53	22.53	0.79	0.00	0.02	0.57	0.03	0.03	20.01	26.29	24.00	0.00	16.00	0.42	0.00	4.95	-2.09	2.86	4.59	-1.73	-0.98
285.00	831.00	48.05	0.00	0.84	6.00	0.02	0.60	0.04	0.04	19.74	26.43	24.00	0.00	17.00	0.42	48.05	1.90	-1.90	0.00	3.37	0.00	0.00
286.00	831.00	61.12	13.07	0.96	0.00	0.02	0.69	0.04	0.04	19.48	26.57	24.00	0.00	18.00	0.42	0.00	6.63	-1.62	5.01	6.20	-1.19	-0.35
287.00	833.00	0.00	0.00	0.87	5.40	0.02	0.62	0.02	0.02	28.03	29.29	29.00	1.00	2.00	-0.18	0.00	0.00	0.00	0.00	0.00	0.00	0.00
288.00	833.00	23.67	0.00	0.87	5.40	0.02	0.62	0.03	0.03	27.69	29.43	29.00	1.00	3.00	-0.18	23.67	4.86	-4.86	0.00	4.33	0.00	0.00
289.00	833.00	47.25	0.00	0.87	5.40	0.02	0.62	0.03	0.03	27.36	29.57	29.00	1.00	4.00	-0.18	23.58	7.51	-7.51	0.00	6.41	0.00	0.00
290.00	833.00	66.08	18.83	0.87	0.00	0.02	0.62	0.03	0.03	27.04	29.71	29.00	1.00	5.00	-0.18	0.00	10.06	-1.12	8.94	6.08	2.86	1.35
291.00	833.00	71.00	0.00	0.87	5.40	0.02	0.62	0.03	0.03	27.04	29.71	29.00	1.00	5.00	-0.18	23.75	8.87	-8.87	0.00	7.33	0.00	0.00
292.00	833.00	82.50	11.50	0.83	0.00	0.02	0.59	0.03	0.03	26.72	29.86	29.00	1.00	6.00	-0.18	0.00	13.73	3.62	17.35	8.44	8.91	3.31
293.00	833.00	95.52	0.00	0.83	5.40	0.02	0.59	0.03	0.03	26.72	29.86	29.00	1.00	6.00	-0.18	24.52	9.80	-9.80	0.00	7.89	0.00	0.00
294.00	833.00	100.32	4.80	0.80	0.00	0.02	0.57	0.03	0.03	26.40	30.00	29.00	1.00	7.00	-0.18	0.00	17.39	-8.50	8.89	10.89	-2.00	-0.70
295.00	833.00	112.42	16.90	0.80	0.00	0.02	0.57	0.03	0.03	26.40	30.00	29.00	1.00	7.00	-0.18	0.00	12.66	-7.09	5.57	7.44	-1.87	-0.94
296.00	833.00	119.32	0.00	0.80	5.40	0.02	0.57	0.03	0.03	26.40	30.00	29.00	1.00	7.00	-0.18	23.80	10.56	-10.56	0.00	8.39	0.00	0.00
297.00	833.00	135.67	16.35	0.85	0.00	0.02	0.61	0.03	0.03	26.09	30.14	29.00	1.00	8.00	-0.18	0.00	12.27	-6.25	6.02	7.17	-1.15	-0.66
298.00	833.00	143.25	0.00	0.85	5.40	0.02	0.61	0.03	0.03	26.09	30.14	29.00	1.00	8.00	-0.18	23.93	10.03	-10.03	0.00	7.89	0.00	0.00

299.00	833.00	148.17	4.92	0.86	0.00	0.02	0.62	0.03	25.79	30.29	29.00	1.00	9.00	-0.18	0.00	16.48	-10.56	5.92	10.17	-4.25	-1.47
300.00	835.00	0.00	0.00	1.86	17.50	0.04	1.33	0.03	20.89	36.86	24.00	0.00	84.00	-0.46	0.00	0.00	0.00	0.00	0.00	0.00	0.00
301.00	835.00	7.32	0.00	1.86	17.50	0.04	1.33	0.03	20.89	36.86	24.00	0.00	84.00	-0.46	7.32	10.49	-10.49	0.00	9.19	0.00	0.00
302.00	835.00	13.75	6.43	1.86	0.00	0.04	1.33	0.03	20.69	37.00	24.00	0.00	85.00	-0.46	0.00	19.24	-9.04	10.20	11.51	-1.31	-1.15
303.00	835.00	15.85	0.00	1.86	17.50	0.04	1.33	0.03	20.69	37.00	24.00	0.00	85.00	-0.46	8.53	17.93	-17.93	0.00	14.43	0.00	0.00
304.00	835.00	24.38	0.00	1.86	17.50	0.04	1.33	0.03	20.69	37.00	24.00	0.00	85.00	-0.46	8.53	23.52	-23.52	0.00	17.77	0.00	0.00
305.00	835.00	32.23	0.00	1.86	17.50	0.04	1.33	0.03	20.69	37.00	24.00	0.00	85.00	-0.46	7.85	28.36	-28.36	0.00	20.62	0.00	0.00
306.00	835.00	38.83	6.60	1.85	0.00	0.04	1.32	0.03	20.49	37.14	24.00	0.00	86.00	-0.46	0.00	33.57	-10.97	22.60	17.18	5.42	-0.17
307.00	835.00	39.27	0.00	1.85	17.50	0.04	1.32	0.03	20.49	37.14	24.00	0.00	86.00	-0.46	7.03	33.07	-33.07	0.00	23.53	0.00	0.00
308.00	835.00	48.12	0.00	1.85	17.50	0.04	1.32	0.03	20.49	37.14	24.00	0.00	86.00	-0.46	8.85	34.49	-34.49	0.00	23.10	0.00	0.00
309.00	835.00	55.58	0.00	1.85	17.50	0.04	1.32	0.03	20.49	37.14	24.00	0.00	86.00	-0.46	7.47	37.24	-37.24	0.00	24.60	0.00	0.00
310.00	835.00	63.17	0.00	1.85	17.50	0.05	1.32	0.03	20.29	37.29	24.00	0.00	87.00	-0.46	7.58	39.12	-39.12	0.00	25.33	0.00	0.00
311.00	835.00	71.92	8.75	1.85	0.00	0.05	1.32	0.03	20.29	37.29	24.00	0.00	87.00	-0.46	0.00	38.99	-7.09	31.90	17.29	14.61	1.08
312.00	835.00	73.87	0.00	1.85	17.50	0.05	1.32	0.03	20.29	37.29	24.00	0.00	87.00	-0.46	10.70	36.48	-36.48	0.00	21.82	0.00	0.00
313.00	835.00	81.73	0.00	1.85	17.50	0.05	1.32	0.03	20.10	37.43	24.00	0.00	88.00	-0.46	7.87	38.08	-38.08	0.00	23.05	0.00	0.00
314.00	835.00	88.93	0.00	1.85	17.50	0.05	1.32	0.03	20.10	37.43	24.00	0.00	88.00	-0.46	7.20	40.20	-40.20	0.00	24.73	0.00	0.00
315.00	835.00	97.50	0.00	1.95	17.50	0.05	1.40	0.03	20.10	37.43	24.00	0.00	88.00	-0.46	8.57	37.88	-37.88	0.00	22.77	0.00	0.00
316.00	835.00	104.78	0.00	1.95	17.50	0.05	1.40	0.03	20.10	37.43	24.00	0.00	88.00	-0.46	7.28	39.40	-39.40	0.00	23.96	0.00	0.00
317.00	835.00	114.18	0.00	1.95	17.50	0.05	1.40	0.03	19.91	37.57	24.00	0.00	89.00	-0.46	9.40	37.61	-37.61	0.00	21.95	0.00	0.00
318.00	835.00	121.35	0.00	1.95	17.50	0.05	1.40	0.03	19.91	37.57	24.00	0.00	89.00	-0.46	7.17	39.25	-39.25	0.00	23.47	0.00	0.00
319.00	835.00	129.82	0.00	1.95	17.50	0.05	1.40	0.04	19.73	37.71	24.00	0.00	90.00	-0.46	8.47	38.63	-38.63	0.00	22.70	0.00	0.00
320.00	835.00	133.58	3.76	2.21	0.00	0.06	1.58	0.04	19.73	37.71	24.00	0.00	90.00	-0.46	0.00	39.74	-2.64	37.10	18.17	18.93	1.99
321.00	836.00	0.00	0.00	3.85	27.50	0.29	2.75	0.10	6.68	40.43	30.00	2.00	71.00	0.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00
322.00	836.00	11.35	0.00	3.85	27.50	0.29	2.75	0.10	6.62	40.57	30.00	2.00	72.00	0.45	11.35	3.21	-3.21	0.00	4.84	0.00	0.00
323.00	836.00	15.02	3.67	3.85	0.00	0.29	2.75	0.10	6.62	40.57	30.00	2.00	72.00	0.45	0.00	9.35	-4.49	4.86	8.47	-3.61	-1.03
324.00	836.00	23.18	0.00	3.85	27.50	0.29	2.75	0.10	6.62	40.57	30.00	2.00	72.00	0.45	11.83	3.98	-3.98	0.00	6.89	0.00	0.00
325.00	836.00	29.02	5.84	3.85	0.00	0.29	2.75	0.11	6.56	40.71	30.00	2.00	73.00	0.45	0.00	7.83	-1.66	6.17	8.29	-2.12	-0.15
326.00	836.00	35.28	0.00	3.85	27.50	0.29	2.75	0.11	6.56	40.71	30.00	2.00	73.00	0.45	12.10	4.05	-4.05	0.00	7.62	0.00	0.00
327.00	836.00	47.65	0.00	3.85	27.50	0.29	2.75	0.11	6.56	40.71	30.00	2.00	73.00	0.45	12.37	3.95	-3.95	0.00	7.81	0.00	0.00
328.00	836.00	59.70	0.00	3.85	27.50	0.29	2.75	0.11	6.51	40.86	30.00	2.00	74.00	0.45	12.05	4.01	-4.01	0.00	8.00	0.00	0.00

329.00	836.00	72.58	0.00	3.85	27.50	0.29	2.75	0.11	6.51	40.86	30.00	2.00	74.00	0.45	12.88	3.69	-3.69	0.00	7.65	0.00	0.00
330.00	836.00	76.43	3.85	3.81	0.00	0.29	2.73	0.11	6.45	41.00	30.00	2.00	75.00	0.45	0.00	9.51	-1.03	8.48	9.95	-1.47	0.24
331.00	836.00	83.18	0.00	3.81	27.50	0.29	2.73	0.11	6.45	41.00	30.00	2.00	75.00	0.45	10.60	4.61	-4.61	0.00	8.79	0.00	0.00
332.00	836.00	95.13	0.00	3.81	27.50	0.29	2.73	0.11	6.45	41.00	30.00	2.00	75.00	0.45	11.95	4.23	-4.23	0.00	8.48	0.00	0.00
333.00	836.00	100.68	5.55	3.68	0.00	0.29	2.63	0.11	6.40	41.14	30.00	2.00	76.00	0.45	0.00	8.44	-5.41	3.03	9.53	-6.50	-1.35
334.00	836.00	107.15	0.00	3.68	27.50	0.29	2.63	0.11	6.40	41.14	30.00	2.00	76.00	0.45	12.02	4.19	-4.19	0.00	8.54	0.00	0.00
335.00	836.00	120.52	0.00	3.68	27.50	0.29	2.63	0.11	6.40	41.14	30.00	2.00	76.00	0.45	13.37	3.58	-3.58	0.00	7.69	0.00	0.00
336.00	836.00	125.10	4.58	3.72	0.00	0.29	2.66	0.11	6.34	41.29	30.00	2.00	77.00	0.45	0.00	8.76	-1.53	7.23	9.49	-2.26	0.02
337.00	840.00	0.00	0.00	1.71	10.00	0.04	1.22	0.04	19.05	31.29	28.00	1.00	23.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00
338.00	840.00	12.00	0.00	1.71	10.00	0.05	1.22	0.04	18.84	31.43	28.00	1.00	24.00	0.04	12.00	5.35	-5.35	0.00	5.44	0.00	0.00
339.00	840.00	23.60	0.00	1.71	10.00	0.05	1.22	0.04	18.84	31.43	28.00	1.00	24.00	0.04	11.60	8.93	-8.93	0.00	9.13	0.00	0.00
340.00	840.00	35.78	0.00	1.71	10.00	0.05	1.22	0.04	18.63	31.57	28.00	1.00	25.00	0.04	12.18	10.97	-10.97	0.00	11.29	0.00	0.00
341.00	840.00	141.88	0.00	1.71	10.00	0.05	1.22	0.04	17.81	32.14	28.00	1.00	29.00	0.04	106.10	0.31	-0.31	0.00	0.37	0.00	0.00
342.00	840.00	151.62	0.00	1.71	10.00	0.05	1.22	0.04	17.62	32.29	28.00	1.00	30.00	0.04	9.73	5.90	-5.90	0.00	6.02	0.00	0.00
343.00	840.00	163.50	0.00	1.71	10.00	0.05	1.22	0.04	17.62	32.29	28.00	1.00	30.00	0.04	11.88	8.92	-8.92	0.00	9.16	0.00	0.00
344.00	840.00	176.75	0.00	1.71	10.00	0.05	1.22	0.04	17.43	32.43	28.00	1.00	31.00	0.04	13.25	10.19	-10.19	0.00	10.54	0.00	0.00
345.00	840.00	187.48	0.00	1.71	10.00	0.05	1.22	0.04	17.43	32.43	28.00	1.00	31.00	0.04	10.73	12.09	-12.09	0.00	12.52	0.00	0.00
346.00	840.00	199.60	0.00	1.71	10.00	0.05	1.22	0.04	17.24	32.57	28.00	1.00	32.00	0.04	12.12	12.55	-12.55	0.00	13.05	0.00	0.00
347.00	840.00	201.67	2.07	1.71	0.00	0.05	1.22	0.04	17.24	32.57	28.00	1.00	32.00	0.04	0.00	19.22	-0.82	18.40	19.74	-1.34	-0.32
348.00	840.00	211.63	0.00	1.71	10.00	0.05	1.22	0.04	17.24	32.57	28.00	1.00	32.00	0.04	12.03	12.88	-12.88	0.00	13.44	0.00	0.00
349.00	840.00	223.72	0.00	1.71	10.00	0.05	1.22	0.04	17.05	32.71	28.00	1.00	33.00	0.04	12.08	12.98	-12.98	0.00	13.57	0.00	0.00
350.00	840.00	235.97	0.00	1.71	10.00	0.05	1.22	0.04	17.05	32.71	28.00	1.00	33.00	0.04	12.25	12.96	-12.96	0.00	13.58	0.00	0.00
351.00	840.00	247.97	0.00	1.71	10.00	0.05	1.22	0.04	16.87	32.86	28.00	1.00	34.00	0.04	12.00	13.01	-13.01	0.00	13.64	0.00	0.00
352.00	840.00	249.50	1.53	1.85	0.00	0.05	1.32	0.04	16.87	32.86	28.00	1.00	34.00	0.04	0.00	18.54	-4.34	14.20	19.12	-4.92	-1.62
353.00	840.00	259.92	0.00	1.85	10.00	0.05	1.32	0.04	16.87	32.86	28.00	1.00	34.00	0.04	11.95	12.08	-12.08	0.00	12.67	0.00	0.00
354.00	840.00	272.03	0.00	1.85	10.00	0.05	1.32	0.04	16.69	33.00	28.00	1.00	35.00	0.04	12.12	11.97	-11.97	0.00	12.57	0.00	0.00
355.00	840.00	283.78	0.00	1.85	10.00	0.05	1.32	0.04	16.69	33.00	28.00	1.00	35.00	0.04	11.75	12.08	-12.08	0.00	12.68	0.00	0.00
356.00	840.00	296.15	0.00	1.85	10.00	0.06	1.32	0.04	16.51	33.14	28.00	1.00	36.00	0.04	12.37	11.78	-11.78	0.00	12.38	0.00	0.00
357.00	840.00	297.58	1.43	2.01	0.00	0.06	1.44	0.04	16.51	33.14	28.00	1.00	36.00	0.04	0.00	16.90	1.50	18.40	17.45	0.95	0.59
358.00	840.00	307.40	0.00	2.01	10.00	0.06	1.44	0.04	16.51	33.14	28.00	1.00	36.00	0.04	11.25	11.19	-11.19	0.00	11.74	0.00	0.00

359.00	840.00	320.18	0.00	2.01	12.50	0.06	1.44	0.04	16.33	33.29	28.00	1.00	37.00	0.04	12.78	10.64	-10.64	0.00	11.19	0.00	0.00
360.00	840.00	332.27	0.00	2.01	12.50	0.06	1.44	0.04	16.33	33.29	28.00	1.00	37.00	0.04	12.08	11.68	-11.68	0.00	12.25	0.00	0.00
361.00	840.00	343.87	0.00	2.01	12.50	0.06	1.44	0.04	16.16	33.43	28.00	1.00	38.00	0.04	11.60	12.50	-12.50	0.00	13.09	0.00	0.00
362.00	840.00	355.70	0.00	2.01	12.50	0.06	1.44	0.04	16.16	33.43	28.00	1.00	38.00	0.04	11.83	12.88	-12.88	0.00	13.49	0.00	0.00
363.00	840.00	367.95	0.00	2.01	12.50	0.06	1.44	0.04	15.99	33.57	28.00	1.00	39.00	0.04	12.25	12.80	-12.80	0.00	13.42	0.00	0.00
364.00	840.00	372.33	4.38	2.19	0.00	0.07	1.56	0.04	15.99	33.57	28.00	1.00	39.00	0.04	0.00	16.48	0.02	16.50	17.08	-0.58	-0.01
365.00	840.00	380.62	0.00	2.19	12.50	0.07	1.56	0.04	15.99	33.57	28.00	1.00	39.00	0.04	12.67	11.51	-11.51	0.00	12.09	0.00	0.00
366.00	840.00	391.98	0.00	2.19	12.50	0.07	1.56	0.04	15.82	33.71	28.00	1.00	40.00	0.04	11.37	11.96	-11.96	0.00	12.55	0.00	0.00
367.00	840.00	394.00	2.02	2.25	0.00	0.07	1.61	0.04	15.82	33.71	28.00	1.00	40.00	0.04	0.00	17.91	2.99	20.90	18.49	2.41	1.12
368.00	1142.00	0.00	0.00	1.92	14.50	0.09	1.37	0.07	10.53	39.57	29.00	1.00	71.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00
369.00	1142.00	10.03	0.00	1.92	14.50	0.09	1.37	0.07	10.53	39.57	29.00	1.00	71.00	0.05	10.03	5.46	-5.46	0.00	5.63	0.00	0.00
370.00	1142.00	18.17	8.14	1.92	0.00	0.09	1.37	0.07	10.44	39.71	29.00	1.00	72.00	0.05	0.00	9.33	-2.33	7.00	6.90	0.10	0.03
371.00	1151.00	0.00	0.00	2.25	25.00	0.15	1.61	0.09	7.62	36.14	28.00	1.00	55.00	0.60	0.00	0.00	0.00	0.00	0.00	0.00	0.00
372.00	1151.00	11.40	0.00	2.25	25.00	0.15	1.61	0.09	7.55	36.29	28.00	1.00	56.00	0.60	11.40	5.45	-5.45	0.00	8.72	0.00	0.00
373.00	1151.00	23.77	0.00	2.25	25.00	0.15	1.61	0.09	7.55	36.29	28.00	1.00	56.00	0.60	12.37	6.74	-6.74	0.00	12.97	0.00	0.00
374.00	1151.00	35.68	0.00	2.25	25.00	0.15	1.61	0.09	7.47	36.43	28.00	1.00	57.00	0.60	11.92	7.38	-7.38	0.00	15.51	0.00	0.00
375.00	1151.00	47.73	0.00	2.25	25.00	0.15	1.61	0.09	7.47	36.43	28.00	1.00	57.00	0.60	12.05	7.49	-7.49	0.00	16.77	0.00	0.00
376.00	1151.00	59.67	0.00	2.25	25.00	0.15	1.61	0.09	7.40	36.57	28.00	1.00	58.00	0.60	11.93	7.53	-7.53	0.00	17.45	0.00	0.00
377.00	1151.00	71.62	0.00	2.25	25.00	0.15	1.61	0.09	7.40	36.57	28.00	1.00	58.00	0.60	11.95	7.53	-7.53	0.00	17.80	0.00	0.00
378.00	1151.00	83.72	0.00	2.25	25.00	0.15	1.61	0.09	7.33	36.71	28.00	1.00	59.00	0.60	12.10	7.34	-7.34	0.00	17.75	0.00	0.00
379.00	1151.00	96.13	0.00	2.25	25.00	0.15	1.61	0.09	7.33	36.71	28.00	1.00	59.00	0.60	12.42	7.07	-7.07	0.00	17.44	0.00	0.00
380.00	1151.00	107.95	0.00	2.25	25.00	0.15	1.61	0.10	7.26	36.86	28.00	1.00	60.00	0.60	11.82	7.31	-7.31	0.00	17.71	0.00	0.00
381.00	1151.00	119.58	0.00	2.25	25.00	0.15	1.61	0.10	7.26	36.86	28.00	1.00	60.00	0.60	11.63	7.52	-7.52	0.00	18.03	0.00	0.00
382.00	1151.00	131.13	11.55	2.25	0.00	0.16	1.61	0.10	7.19	37.00	28.00	1.00	61.00	0.60	0.00	7.57	-2.67	4.90	12.96	-8.06	-0.95
383.00	1160.00	0.00	0.00	2.14	21.00	0.07	1.53	0.05	15.36	38.71	24.00	0.00	97.00	-0.28	0.00	0.00	0.00	0.00	0.00	0.00	0.00
384.00	1160.00	7.57	0.00	2.14	21.00	0.07	1.53	0.05	15.36	38.71	24.00	0.00	97.00	-0.28	7.57	9.77	-9.77	0.00	8.77	0.00	0.00
385.00	1160.00	14.35	6.78	2.14	0.00	0.07	1.53	0.05	15.22	38.86	24.00	0.00	98.00	-0.28	0.00	17.26	-10.11	7.15	10.69	-3.54	-1.64
386.00	1160.00	16.00	0.00	2.14	21.00	0.07	1.53	0.05	15.22	38.86	24.00	0.00	98.00	-0.28	8.43	16.01	-16.01	0.00	13.58	0.00	0.00
387.00	1160.00	24.17	0.00	2.14	21.00	0.07	1.53	0.05	15.22	38.86	24.00	0.00	98.00	-0.28	8.17	20.51	-20.51	0.00	16.74	0.00	0.00
388.00	1160.00	31.47	0.00	2.14	21.00	0.07	1.53	0.05	15.22	38.86	24.00	0.00	98.00	-0.28	7.30	24.57	-24.57	0.00	19.68	0.00	0.00



389.00	1160.00	39.65	0.00	2.14	21.00	0.07	1.53	0.05	15.09	39.00	24.00	0.00	99.00	-0.28	8.18	26.31	-26.31	0.00	20.38	0.00	0.00
390.00	1160.00	47.87	0.00	2.14	21.00	0.07	1.53	0.05	15.09	39.00	24.00	0.00	99.00	-0.28	8.22	27.45	-27.45	0.00	20.76	0.00	0.00
391.00	1160.00	56.02	0.00	2.14	21.00	0.07	1.53	0.05	15.09	39.00	24.00	0.00	99.00	-0.28	8.15	28.33	-28.33	0.00	21.07	0.00	0.00
392.00	1160.00	63.45	0.00	2.14	21.00	0.07	1.53	0.05	14.95	39.14	24.00	0.00	100.00	-0.28	7.43	29.81	-29.81	0.00	22.12	0.00	0.00
393.00	1160.00	71.57	0.00	2.14	21.00	0.07	1.53	0.05	14.95	39.14	24.00	0.00	100.00	-0.28	8.12	29.89	-29.89	0.00	21.85	0.00	0.00
394.00	1160.00	81.33	0.00	2.14	21.00	0.07	1.53	0.05	14.95	39.14	24.00	0.00	100.00	-0.28	9.77	27.75	-27.75	0.00	19.62	0.00	0.00
395.00	1160.00	86.27	4.94	2.16	0.00	0.07	1.54	0.05	14.81	39.29	24.00	0.00	101.00	-0.28	0.00	32.60	-5.15	27.45	17.37	10.08	0.98
396.00	1160.00	87.53	0.00	2.16	21.00	0.07	1.54	0.05	14.81	39.29	24.00	0.00	101.00	-0.28	6.20	30.73	-30.73	0.00	22.54	0.00	0.00
397.00	1160.00	95.90	0.00	2.16	21.00	0.07	1.54	0.05	14.81	39.29	24.00	0.00	101.00	-0.28	8.37	29.97	-29.97	0.00	21.58	0.00	0.00
398.00	1160.00	103.88	0.00	2.16	21.00	0.07	1.54	0.05	14.81	39.29	24.00	0.00	101.00	-0.28	7.98	30.00	-30.00	0.00	21.52	0.00	0.00
399.00	1160.00	112.08	0.00	2.16	21.00	0.07	1.54	0.05	14.68	39.43	24.00	0.00	102.00	-0.28	8.20	29.60	-29.60	0.00	21.10	0.00	0.00
400.00	1160.00	120.25	0.00	2.16	21.00	0.07	1.54	0.05	14.68	39.43	24.00	0.00	102.00	-0.28	8.17	29.38	-29.38	0.00	20.89	0.00	0.00
401.00	1160.00	128.02	0.00	2.16	21.00	0.07	1.54	0.05	14.68	39.43	24.00	0.00	102.00	-0.28	7.77	29.78	-29.78	0.00	21.28	0.00	0.00
402.00	1160.00	135.57	0.00	2.16	21.00	0.07	1.54	0.05	14.55	39.57	24.00	0.00	103.00	-0.28	7.55	30.28	-30.28	0.00	21.73	0.00	0.00
403.00	1160.00	144.12	0.00	2.16	21.00	0.07	1.54	0.05	14.55	39.57	24.00	0.00	103.00	-0.28	8.55	29.20	-29.20	0.00	20.67	0.00	0.00
404.00	1160.00	151.50	0.00	2.16	21.00	0.07	1.54	0.05	14.55	39.57	24.00	0.00	103.00	-0.28	7.38	30.12	-30.12	0.00	21.57	0.00	0.00
405.00	1160.00	159.28	0.00	2.16	21.00	0.07	1.54	0.05	14.42	39.71	24.00	0.00	104.00	-0.28	7.78	30.08	-30.08	0.00	21.50	0.00	0.00
406.00	1160.00	168.02	0.00	2.16	21.00	0.07	1.54	0.05	14.42	39.71	24.00	0.00	104.00	-0.28	8.73	28.70	-28.70	0.00	20.19	0.00	0.00
407.00	1160.00	169.43	1.41	2.37	0.00	0.08	1.69	0.05	14.42	39.71	24.00	0.00	104.00	-0.28	0.00	36.09	-5.18	30.90	20.12	10.78	1.05
408.00	1169.00	0.00	0.00	3.61	35.00	0.27	2.58	0.11	6.52	42.57	28.00	1.00	97.00	0.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00
409.00	1169.00	11.48	0.00	3.61	35.00	0.28	2.58	0.11	6.46	42.71	28.00	1.00	98.00	0.35	11.48	3.96	-3.96	0.00	5.68	0.00	0.00
410.00	1169.00	23.10	0.00	3.61	35.00	0.28	2.58	0.11	6.46	42.71	28.00	1.00	98.00	0.35	11.62	5.04	-5.04	0.00	7.97	0.00	0.00
411.00	1169.00	36.07	0.00	3.61	35.00	0.28	2.58	0.11	6.41	42.86	28.00	1.00	99.00	0.35	12.97	4.58	-4.58	0.00	7.98	0.00	0.00
412.00	1169.00	36.60	0.53	3.61	0.00	0.28	2.58	0.11	6.41	42.86	28.00	1.00	99.00	0.35	0.00	17.13	-13.71	3.42	14.75	-11.33	-2.08
413.00	1169.00	47.57	0.00	3.61	35.00	0.28	2.58	0.11	6.41	42.86	28.00	1.00	99.00	0.35	11.50	5.23	-5.23	0.00	8.94	0.00	0.00
414.00	1169.00	59.82	0.00	3.61	35.00	0.28	2.58	0.11	6.36	43.00	28.00	1.00	100.00	0.35	12.25	4.95	-4.95	0.00	8.75	0.00	0.00
415.00	1169.00	71.43	0.00	3.61	35.00	0.28	2.58	0.11	6.36	43.00	28.00	1.00	100.00	0.35	11.62	5.22	-5.22	0.00	9.11	0.00	0.00
416.00	1169.00	83.45	0.00	3.61	35.00	0.28	2.58	0.11	6.31	43.14	28.00	1.00	101.00	0.35	12.02	5.01	-5.01	0.00	8.91	0.00	0.00
417.00	1169.00	95.38	0.00	3.61	35.00	0.28	2.58	0.11	6.31	43.14	28.00	1.00	101.00	0.35	11.93	5.01	-5.01	0.00	8.89	0.00	0.00
418.00	1169.00	107.08	0.00	3.61	35.00	0.29	2.58	0.11	6.25	43.29	28.00	1.00	102.00	0.35	11.70	5.08	-5.08	0.00	8.97	0.00	0.00

419.00	1169.00	120.05	0.00	3.61	35.00	0.29	2.58	0.11	6.25	43.29	28.00	1.00	102.00	0.35	12.97	4.43	-4.43	0.00	8.15	0.00	0.00
420.00	1169.00	131.90	0.00	3.61	35.00	0.29	2.58	0.11	6.20	43.43	28.00	1.00	103.00	0.35	11.85	4.79	-4.79	0.00	8.51	0.00	0.00
421.00	1169.00	143.18	0.00	3.61	35.00	0.29	2.58	0.11	6.20	43.43	28.00	1.00	103.00	0.35	11.28	5.20	-5.20	0.00	9.05	0.00	0.00
422.00	1169.00	155.50	0.00	3.61	35.00	0.29	2.58	0.11	6.15	43.57	28.00	1.00	104.00	0.35	12.32	4.69	-4.69	0.00	8.47	0.00	0.00
423.00	1169.00	168.68	0.00	3.61	35.00	0.29	2.58	0.11	6.15	43.57	28.00	1.00	104.00	0.35	13.18	4.14	-4.14	0.00	7.71	0.00	0.00
424.00	1169.00	179.65	0.00	3.61	35.00	0.29	2.58	0.11	6.10	43.71	28.00	1.00	105.00	0.35	10.97	5.09	-5.09	0.00	8.81	0.00	0.00
425.00	1169.00	191.92	0.00	3.61	35.00	0.29	2.58	0.11	6.10	43.71	28.00	1.00	105.00	0.35	12.27	4.63	-4.63	0.00	8.35	0.00	0.00
426.00	1169.00	203.93	0.00	3.61	35.00	0.30	2.58	0.11	6.05	43.86	28.00	1.00	106.00	0.35	12.02	4.60	-4.60	0.00	8.28	0.00	0.00
427.00	1169.00	205.10	1.17	3.73	0.00	0.31	2.67	0.11	6.05	43.86	28.00	1.00	106.00	0.35	0.00	15.38	-3.78	11.60	13.72	-2.12	0.10
428.00	1192.00	0.00	0.00	2.15	16.00	0.19	1.54	0.12	5.71	37.71	24.00	0.00	92.00	0.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00
429.00	1192.00	10.67	0.00	2.15	16.00	0.19	1.54	0.12	5.71	37.71	24.00	0.00	92.00	0.78	10.67	2.85	-2.85	0.00	5.74	0.00	0.00
430.00	1192.00	22.67	0.00	2.15	16.00	0.19	1.54	0.12	5.65	37.86	24.00	0.00	93.00	0.78	12.00	3.04	-3.04	0.00	8.22	0.00	0.00
431.00	1192.00	34.40	0.00	2.15	16.00	0.19	1.54	0.12	5.65	37.86	24.00	0.00	93.00	0.78	11.73	3.19	-3.19	0.00	9.63	0.00	0.00
432.00	1192.00	43.88	9.48	2.15	0.00	0.19	1.54	0.12	5.60	38.00	24.00	0.00	94.00	0.78	0.00	4.21	-2.40	1.81	8.34	-6.53	-1.23
433.00	1192.00	45.90	0.00	2.15	16.00	0.19	1.54	0.12	5.60	38.00	24.00	0.00	94.00	0.78	11.50	3.28	-3.28	0.00	10.43	0.00	0.00
434.00	1192.00	58.85	0.00	2.15	16.00	0.19	1.54	0.12	5.60	38.00	24.00	0.00	94.00	0.78	12.95	2.76	-2.76	0.00	9.99	0.00	0.00
435.00	1192.00	70.30	0.00	2.15	16.00	0.19	1.54	0.12	5.55	38.14	24.00	0.00	95.00	0.78	11.45	3.15	-3.15	0.00	10.59	0.00	0.00
436.00	1192.00	81.85	0.00	2.15	16.00	0.19	1.54	0.12	5.55	38.14	24.00	0.00	95.00	0.78	11.55	3.20	-3.20	0.00	10.83	0.00	0.00
437.00	1192.00	94.32	0.00	2.15	16.00	0.19	1.54	0.13	5.50	38.29	24.00	0.00	96.00	0.78	12.47	2.82	-2.82	0.00	10.33	0.00	0.00
438.00	1192.00	106.43	0.00	2.15	16.00	0.19	1.54	0.13	5.50	38.29	24.00	0.00	96.00	0.78	12.12	2.87	-2.87	0.00	10.29	0.00	0.00
439.00	1192.00	114.43	8.00	2.24	0.00	0.20	1.60	0.13	5.45	38.43	24.00	0.00	97.00	0.78	0.00	4.62	-0.26	4.36	8.90	-4.55	-0.26
440.00	1192.00	118.70	0.00	2.24	16.00	0.20	1.60	0.13	5.45	38.43	24.00	0.00	97.00	0.78	12.27	2.68	-2.68	0.00	9.73	0.00	0.00
441.00	1192.00	130.40	0.00	2.24	16.00	0.20	1.60	0.13	5.45	38.43	24.00	0.00	97.00	0.78	11.70	2.86	-2.86	0.00	9.97	0.00	0.00
442.00	1192.00	144.13	0.00	2.24	16.00	0.21	1.60	0.13	5.40	38.57	24.00	0.00	98.00	0.78	13.73	2.21	-2.21	0.00	8.90	0.00	0.00
443.00	1192.00	154.57	0.00	2.24	16.00	0.21	1.60	0.13	5.40	38.57	24.00	0.00	98.00	0.78	10.43	3.20	-3.20	0.00	10.23	0.00	0.00
444.00	1192.00	166.02	0.00	2.24	16.00	0.21	1.60	0.13	5.35	38.71	24.00	0.00	99.00	0.78	11.45	2.99	-2.99	0.00	10.25	0.00	0.00
445.00	1192.00	177.92	0.00	2.24	16.00	0.21	1.60	0.13	5.35	38.71	24.00	0.00	99.00	0.78	11.90	2.78	-2.78	0.00	9.99	0.00	0.00
446.00	1192.00	190.42	0.00	2.24	16.00	0.21	1.60	0.13	5.30	38.86	24.00	0.00	100.00	0.78	12.50	2.49	-2.49	0.00	9.45	0.00	0.00
447.00	1192.00	202.45	0.00	2.24	16.00	0.21	1.60	0.13	5.30	38.86	24.00	0.00	100.00	0.78	12.03	2.59	-2.59	0.00	9.46	0.00	0.00
448.00	1192.00	210.33	7.88	2.34	0.00	0.22	1.67	0.13	5.25	39.00	24.00	0.00	101.00	0.78	0.00	4.26	-1.78	2.48	8.25	-5.77	-0.81

449.00	2114.00	0.00	0.00	2.69	20.00	0.17	1.92	0.09	8.06	38.43	28.00	1.00	73.00	0.39	0.00	0.00	0.00	0.00	0.00	0.00
450.00	2114.00	5.08	0.00	2.69	20.00	0.17	1.92	0.09	7.99	38.57	28.00	1.00	74.00	0.39	5.08	6.84	-6.84	0.00	7.82	0.00
451.00	2114.00	11.25	0.00	2.66	20.00	0.17	1.90	0.09	7.99	38.57	28.00	1.00	74.00	0.39	6.17	10.34	-10.34	0.00	12.92	0.00
452.00	2114.00	17.50	0.00	2.66	20.00	0.17	1.90	0.09	7.99	38.57	28.00	1.00	74.00	0.39	6.25	12.26	-12.26	0.00	16.33	0.00
453.00	2114.00	24.42	0.00	2.66	20.00	0.17	1.90	0.09	7.99	38.57	28.00	1.00	74.00	0.39	6.92	12.62	-12.62	0.00	17.96	0.00
454.00	2114.00	29.50	0.00	2.66	20.00	0.17	1.90	0.09	7.92	38.71	28.00	1.00	75.00	0.39	5.08	14.98	-14.98	0.00	21.17	0.00
455.00	2114.00	30.10	0.60	2.69	0.00	0.17	1.92	0.09	7.92	38.71	28.00	1.00	75.00	0.39	0.00	24.13	-5.43	18.70	21.67	-0.10
456.00	2114.00	35.25	0.00	2.69	20.00	0.17	1.92	0.09	7.92	38.71	28.00	1.00	75.00	0.39	5.75	15.37	-15.37	0.00	22.38	0.00
457.00	2114.00	41.25	0.00	2.69	20.00	0.17	1.92	0.09	7.92	38.71	28.00	1.00	75.00	0.39	6.00	15.37	-15.37	0.00	23.06	0.00
458.00	2114.00	47.67	0.00	2.69	20.00	0.17	1.92	0.09	7.92	38.71	28.00	1.00	75.00	0.39	6.42	14.82	-14.82	0.00	22.95	0.00
459.00	2114.00	53.25	0.00	2.69	20.00	0.17	1.92	0.09	7.84	38.86	28.00	1.00	76.00	0.39	5.58	15.54	-15.54	0.00	23.98	0.00
460.00	2114.00	59.25	0.00	2.69	20.00	0.17	1.92	0.09	7.84	38.86	28.00	1.00	76.00	0.39	6.00	15.40	-15.40	0.00	24.10	0.00
461.00	2114.00	65.25	0.00	2.69	20.00	0.17	1.92	0.09	7.84	38.86	28.00	1.00	76.00	0.39	6.00	15.32	-15.32	0.00	24.18	0.00
462.00	2114.00	71.25	0.00	2.69	20.00	0.17	1.92	0.09	7.84	38.86	28.00	1.00	76.00	0.39	6.00	15.27	-15.27	0.00	24.24	0.00
463.00	2114.00	77.25	0.00	2.69	20.00	0.17	1.92	0.09	7.77	39.00	28.00	1.00	77.00	0.39	6.00	15.17	-15.17	0.00	24.20	0.00
464.00	2114.00	79.25	2.00	2.73	0.00	0.17	1.95	0.09	7.77	39.00	28.00	1.00	77.00	0.39	0.00	21.27	-2.47	18.80	21.64	0.14
465.00	2114.00	83.25	0.00	2.73	20.00	0.17	1.95	0.09	7.77	39.00	28.00	1.00	77.00	0.39	6.00	14.89	-14.89	0.00	23.82	0.00
466.00	2114.00	88.53	5.28	2.73	0.00	0.17	1.95	0.09	7.77	39.00	28.00	1.00	77.00	0.39	0.00	15.84	-5.34	10.50	17.73	-0.57
467.00	2114.00	89.25	0.00	2.73	20.00	0.17	1.95	0.09	7.77	39.00	28.00	1.00	77.00	0.39	6.00	14.85	-14.85	0.00	23.81	0.00
468.00	2114.00	95.75	0.00	2.73	20.00	0.17	1.95	0.09	7.77	39.00	28.00	1.00	77.00	0.39	6.50	14.19	-14.19	0.00	23.08	0.00
469.00	2114.00	101.55	0.00	2.73	20.00	0.18	1.95	0.09	7.70	39.14	28.00	1.00	78.00	0.39	5.80	14.63	-14.63	0.00	23.50	0.00
470.00	2114.00	103.25	1.70	2.73	0.00	0.18	1.95	0.09	7.70	39.14	28.00	1.00	78.00	0.39	0.00	21.55	-8.85	12.70	21.79	-0.77
471.00	6128.00	0.00	0.00	1.19	17.90	0.02	0.85	0.03	24.52	29.29	29.00	1.00	2.00	-0.05	0.00	0.00	0.00	0.00	0.00	0.00
472.00	6128.00	15.00	0.00	1.19	17.90	0.02	0.85	0.03	24.22	29.43	29.00	1.00	3.00	-0.05	15.00	13.95	-13.95	0.00	13.66	0.00
473.00	6128.00	19.50	4.50	1.19	0.00	0.02	0.85	0.03	24.22	29.43	29.00	1.00	3.00	-0.05	0.00	31.09	-7.59	23.50	21.86	1.64
474.00	6128.00	27.00	0.00	1.19	17.90	0.02	0.85	0.03	24.22	29.43	29.00	1.00	3.00	-0.05	12.00	25.09	-25.09	0.00	24.47	0.00
475.00	6128.00	39.00	0.00	1.19	17.90	0.02	0.85	0.03	23.93	29.57	29.00	1.00	4.00	-0.05	12.00	32.86	-32.86	0.00	31.88	0.00
476.00	6128.00	43.50	4.50	1.20	0.00	0.02	0.86	0.03	23.93	29.57	29.00	1.00	4.00	-0.05	0.00	47.17	-6.67	40.50	32.83	7.67
477.00	6128.00	51.00	0.00	1.20	17.90	0.02	0.86	0.03	23.93	29.57	29.00	1.00	4.00	-0.05	12.00	37.96	-37.96	0.00	36.65	0.00
478.00	6128.00	65.00	0.00	1.20	17.90	0.03	0.86	0.03	23.65	29.71	29.00	1.00	5.00	-0.05	14.00	39.26	-39.26	0.00	37.62	0.00

479.00	6128.00	75.25	10.25	1.21	0.00	0.03	0.87	0.03	23.65	29.71	29.00	1.00	5.00	-0.05	0.00	44.34	-24.14	20.20	30.31	-10.11	-1.23
480.00	6128.00	77.00	0.00	1.21	17.90	0.03	0.87	0.03	23.65	29.71	29.00	1.00	5.00	-0.05	12.00	42.12	-42.12	0.00	40.28	0.00	0.00
481.00	6128.00	89.00	0.00	1.21	17.90	0.03	0.87	0.03	23.37	29.86	29.00	1.00	6.00	-0.05	12.00	44.22	-44.22	0.00	42.19	0.00	0.00
482.00	6128.00	91.08	2.08	1.13	0.00	0.02	0.81	0.03	23.37	29.86	29.00	1.00	6.00	-0.05	0.00	65.38	-4.68	60.70	45.05	15.66	1.03
483.00	6128.00	101.00	0.00	1.13	17.90	0.02	0.81	0.03	23.37	29.86	29.00	1.00	6.00	-0.05	12.00	48.72	-48.72	0.00	46.38	0.00	0.00
484.00	6128.00	113.00	0.00	1.13	17.90	0.02	0.81	0.03	23.09	30.00	29.00	1.00	7.00	-0.05	12.00	49.61	-49.61	0.00	47.13	0.00	0.00
485.00	6161.00	0.00	0.00	0.68	9.60	0.01	0.49	0.02	32.10	25.29	24.00	0.00	9.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00
486.00	6161.00	7.25	7.25	0.68	0.00	0.01	0.49	0.02	31.66	25.43	24.00	0.00	10.00	0.05	0.00	17.07	-3.59	13.48	12.26	1.22	0.34
487.00	6161.00	12.00	0.00	0.68	9.60	0.01	0.49	0.02	31.66	25.43	24.00	0.00	10.00	0.05	12.00	15.39	-15.39	0.00	15.56	0.00	0.00
488.00	6161.00	24.00	0.00	0.68	9.60	0.01	0.49	0.02	31.66	25.43	24.00	0.00	10.00	0.05	12.00	27.22	-27.22	0.00	27.68	0.00	0.00
489.00	6161.00	36.00	0.00	0.65	9.60	0.01	0.47	0.02	31.22	25.57	24.00	0.00	11.00	0.05	12.00	37.57	-37.57	0.00	38.39	0.00	0.00
490.00	6161.00	48.00	0.00	0.65	9.60	0.01	0.47	0.02	31.22	25.57	24.00	0.00	11.00	0.05	12.00	44.70	-44.70	0.00	45.88	0.00	0.00
491.00	6161.00	56.00	8.00	0.73	0.00	0.01	0.52	0.02	30.79	25.71	24.00	0.00	12.00	0.05	0.00	49.19	-23.99	25.20	36.01	-10.81	-1.02
492.00	6161.00	60.00	0.00	0.73	9.60	0.01	0.52	0.02	30.79	25.71	24.00	0.00	12.00	0.05	12.00	44.96	-44.96	0.00	46.33	0.00	0.00
493.00	6161.00	72.00	0.00	0.73	9.60	0.01	0.52	0.02	30.79	25.71	24.00	0.00	12.00	0.05	12.00	48.58	-48.58	0.00	50.24	0.00	0.00
494.00	6161.00	80.00	8.00	0.73	0.00	0.01	0.52	0.02	30.37	25.86	24.00	0.00	13.00	0.05	0.00	56.05	-4.85	51.20	41.30	9.90	0.78
495.00	6161.00	84.00	0.00	0.73	9.60	0.01	0.52	0.02	30.37	25.86	24.00	0.00	13.00	0.05	12.00	51.16	-51.16	0.00	53.08	0.00	0.00
496.00	6161.00	96.00	0.00	0.73	9.60	0.01	0.52	0.02	30.37	25.86	24.00	0.00	13.00	0.05	12.00	53.12	-53.12	0.00	55.26	0.00	0.00
497.00	6161.00	104.00	8.00	0.73	0.00	0.01	0.52	0.02	29.95	26.00	24.00	0.00	14.00	0.05	0.00	59.68	-14.38	45.30	44.20	1.10	0.06
498.00	6161.00	108.00	0.00	0.73	9.60	0.01	0.52	0.02	29.95	26.00	24.00	0.00	14.00	0.05	12.00	54.41	-54.41	0.00	56.74	0.00	0.00
499.00	6161.00	120.00	0.00	0.73	9.60	0.01	0.52	0.02	29.95	26.00	24.00	0.00	14.00	0.05	12.00	55.38	-55.38	0.00	57.87	0.00	0.00
500.00	6161.00	128.25	8.25	0.67	0.00	0.01	0.48	0.02	29.55	26.14	24.00	0.00	15.00	0.05	0.00	65.86	-17.46	48.40	48.97	-0.57	-0.06
501.00	6261.00	0.00	0.00	0.94	9.50	0.02	0.67	0.03	20.53	32.29	24.00	0.00	53.00	-0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00
502.00	6261.00	8.00	0.00	0.94	9.50	0.02	0.67	0.03	20.30	32.43	24.00	0.00	54.00	-0.11	8.00	10.91	-10.91	0.00	10.58	0.00	0.00
503.00	6261.00	15.00	0.00	0.94	9.50	0.02	0.67	0.03	20.30	32.43	24.00	0.00	54.00	-0.11	7.00	19.89	-19.89	0.00	19.09	0.00	0.00
504.00	6261.00	23.00	0.00	0.94	9.50	0.02	0.67	0.03	20.30	32.43	24.00	0.00	54.00	-0.11	8.00	26.05	-26.05	0.00	24.64	0.00	0.00
505.00	6261.00	31.00	0.00	0.94	9.50	0.02	0.67	0.03	20.08	32.57	24.00	0.00	55.00	-0.11	8.00	30.65	-30.65	0.00	28.64	0.00	0.00
506.00	6261.00	35.50	4.50	0.94	0.00	0.02	0.67	0.03	20.08	32.57	24.00	0.00	55.00	-0.11	0.00	38.52	-3.32	35.20	36.14	-0.94	-0.63
507.00	6261.00	39.00	0.00	0.94	9.50	0.02	0.67	0.03	20.08	32.57	24.00	0.00	55.00	-0.11	8.00	34.14	-34.14	0.00	31.57	0.00	0.00
508.00	6261.00	47.00	0.00	0.94	9.50	0.02	0.67	0.03	20.08	32.57	24.00	0.00	55.00	-0.11	8.00	36.78	-36.78	0.00	33.72	0.00	0.00

509.00	6261.00	54.92	7.92	1.04	0.00	0.03	0.74	0.03	20.08	32.57	24.00	0.00	55.00	-0.11	0.00	35.20	2.90	38.10	32.04	6.06	0.68
510.00	6261.00	55.00	0.00	1.04	9.50	0.03	0.74	0.03	19.87	32.71	24.00	0.00	56.00	-0.11	8.00	35.10	-35.10	0.00	31.94	0.00	0.00
511.00	6261.00	63.00	0.00	1.04	9.50	0.03	0.74	0.03	19.87	32.71	24.00	0.00	56.00	-0.11	8.00	36.37	-36.37	0.00	32.88	0.00	0.00
512.00	6261.00	71.00	0.00	1.04	9.50	0.03	0.74	0.03	19.87	32.71	24.00	0.00	56.00	-0.11	8.00	37.34	-37.34	0.00	33.57	0.00	0.00
513.00	6261.00	79.00	0.00	1.04	9.50	0.03	0.74	0.04	19.65	32.86	24.00	0.00	57.00	-0.11	8.00	37.95	-37.95	0.00	33.96	0.00	0.00
514.00	6261.00	85.17	6.17	1.00	0.00	0.03	0.71	0.04	19.65	32.86	24.00	0.00	57.00	-0.11	0.00	42.74	1.06	43.80	38.40	5.40	0.28
515.00	6262.00	0.00	0.00	0.98	9.50	0.03	0.70	0.04	18.33	32.29	24.00	0.00	53.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
516.00	6262.00	8.00	0.00	0.98	9.50	0.03	0.70	0.04	18.13	32.43	24.00	0.00	54.00	0.00	8.00	10.15	-10.15	0.00	10.15	0.00	0.00
517.00	6262.00	16.00	0.00	0.98	9.50	0.03	0.70	0.04	18.13	32.43	24.00	0.00	54.00	0.00	8.00	17.63	-17.63	0.00	17.63	0.00	0.00
518.00	6262.00	24.00	0.00	0.98	9.50	0.03	0.70	0.04	18.13	32.43	24.00	0.00	54.00	0.00	8.00	23.14	-23.14	0.00	23.13	0.00	0.00
519.00	6262.00	32.00	0.00	0.98	9.50	0.03	0.70	0.04	17.93	32.57	24.00	0.00	55.00	0.00	8.00	27.10	-27.10	0.00	27.10	0.00	0.00
520.00	6262.00	36.17	4.17	0.98	0.00	0.03	0.70	0.04	17.93	32.57	24.00	0.00	55.00	0.00	0.00	34.80	0.40	35.20	34.80	0.40	0.07
521.00	6262.00	40.00	0.00	0.98	9.50	0.03	0.70	0.04	17.93	32.57	24.00	0.00	55.00	0.00	8.00	30.01	-30.01	0.00	30.01	0.00	0.00
522.00	6262.00	48.00	0.00	0.98	9.50	0.03	0.70	0.04	17.93	32.57	24.00	0.00	55.00	0.00	8.00	32.15	-32.15	0.00	32.15	0.00	0.00
523.00	6262.00	56.00	0.00	0.98	9.50	0.03	0.70	0.04	17.74	32.71	24.00	0.00	56.00	0.00	8.00	33.61	-33.61	0.00	33.61	0.00	0.00
524.00	6262.00	62.50	6.50	0.98	0.00	0.03	0.70	0.04	17.74	32.71	24.00	0.00	56.00	0.00	0.00	36.69	-5.69	31.00	36.69	-5.69	-1.10
525.00	6262.00	64.00	0.00	0.98	9.50	0.03	0.70	0.04	17.74	32.71	24.00	0.00	56.00	0.00	8.00	34.60	-34.60	0.00	34.60	0.00	0.00
526.00	6262.00	72.00	0.00	0.98	9.50	0.03	0.70	0.04	17.74	32.71	24.00	0.00	56.00	0.00	8.00	35.38	-35.38	0.00	35.38	0.00	0.00
527.00	6262.00	80.00	0.00	0.98	9.50	0.03	0.70	0.04	17.55	32.86	24.00	0.00	57.00	0.00	8.00	35.83	-35.83	0.00	35.83	0.00	0.00
528.00	6262.00	86.17	6.17	1.00	0.00	0.03	0.72	0.04	17.55	32.86	24.00	0.00	57.00	0.00	0.00	38.09	5.21	43.30	38.09	5.21	0.92
529.00	11152.00	0.00	0.00	1.66	12.00	0.07	1.19	0.06	11.26	35.71	31.00	2.00	33.00	0.24	0.00	0.00	0.00	0.00	0.00	0.00	0.00
530.00	11152.00	16.05	16.05	1.66	0.00	0.07	1.19	0.06	11.15	35.86	31.00	2.00	34.00	0.24	0.00	3.85	0.37	4.22	3.36	0.86	1.38
531.00	11152.00	23.13	0.00	1.66	12.00	0.07	1.19	0.06	11.15	35.86	31.00	2.00	34.00	0.24	23.13	2.48	-2.48	0.00	3.33	0.00	0.00
532.00	11152.00	46.72	0.00	1.66	12.00	0.07	1.19	0.06	11.04	36.00	31.00	2.00	35.00	0.24	23.58	2.94	-2.94	0.00	4.26	0.00	0.00
533.00	11152.00	54.27	0.00	1.66	15.00	0.07	1.19	0.06	11.04	36.00	31.00	2.00	35.00	0.24	7.55	8.33	-8.33	0.00	10.06	0.00	0.00
534.00	11152.00	61.72	0.00	1.66	15.00	0.08	1.19	0.06	10.93	36.14	31.00	2.00	36.00	0.24	7.45	13.08	-13.08	0.00	15.64	0.00	0.00
535.00	11152.00	70.10	0.00	1.66	15.00	0.08	1.19	0.06	10.93	36.14	31.00	2.00	36.00	0.24	8.38	15.13	-15.13	0.00	18.60	0.00	0.00
536.00	11152.00	77.98	0.00	1.66	15.00	0.08	1.19	0.06	10.93	36.14	31.00	2.00	36.00	0.24	7.88	16.86	-16.86	0.00	21.06	0.00	0.00
537.00	11152.00	86.38	0.00	1.66	15.00	0.08	1.19	0.06	10.82	36.29	31.00	2.00	37.00	0.24	8.40	17.23	-17.23	0.00	22.05	0.00	0.00
538.00	11152.00	89.65	3.27	1.70	0.00	0.08	1.22	0.06	10.82	36.29	31.00	2.00	37.00	0.24	0.00	23.64	-8.04	15.60	20.46	-4.86	-0.30

539.00	11152.00	94.57	0.00	1.70	15.00	0.08	1.22	0.06	10.82	36.29	31.00	2.00	37.00	0.24	8.18	17.25	-17.25	0.00	22.37	0.00	0.00
540.00	11152.00	101.77	0.00	1.70	15.00	0.08	1.22	0.06	10.82	36.29	31.00	2.00	37.00	0.24	7.20	18.66	-18.66	0.00	24.12	0.00	0.00
541.00	11152.00	105.18	3.41	1.71	0.00	0.08	1.22	0.06	10.82	36.29	31.00	2.00	37.00	0.24	0.00	24.85	-3.05	21.80	21.82	-0.02	0.50
542.00	11152.00	110.03	0.00	1.71	15.00	0.08	1.22	0.06	10.72	36.43	31.00	2.00	38.00	0.24	8.27	18.16	-18.16	0.00	23.88	0.00	0.00
543.00	11152.00	118.05	8.02	1.71	0.00	0.08	1.22	0.06	10.72	36.43	31.00	2.00	38.00	0.24	0.00	18.14	-7.24	10.90	17.14	-6.24	-0.46
544.00	11152.00	118.85	0.00	1.71	15.00	0.08	1.22	0.06	10.72	36.43	31.00	2.00	38.00	0.24	8.82	17.22	-17.22	0.00	23.07	0.00	0.00
545.00	11152.00	130.70	0.00	1.71	13.00	0.08	1.22	0.06	10.72	36.43	31.00	2.00	38.00	0.24	11.85	13.72	-13.72	0.00	19.32	0.00	0.00
546.00	11152.00	138.80	8.10	1.71	0.00	0.08	1.22	0.07	10.62	36.57	31.00	2.00	39.00	0.24	0.00	14.58	-8.78	5.80	14.21	-8.41	-1.03
547.00	11152.00	141.65	0.00	1.71	13.00	0.08	1.22	0.07	10.62	36.57	31.00	2.00	39.00	0.24	10.95	12.10	-12.10	0.00	17.20	0.00	0.00
548.00	11152.00	145.40	3.75	1.64	0.00	0.08	1.17	0.07	10.62	36.57	31.00	2.00	39.00	0.24	0.00	18.87	-9.77	9.10	17.25	-8.15	-0.85
549.00	11152.00	153.72	0.00	1.64	13.00	0.08	1.17	0.07	10.62	36.57	31.00	2.00	39.00	0.24	12.07	10.96	-10.96	0.00	15.75	0.00	0.00
550.00	11152.00	161.47	7.75	1.64	0.00	0.08	1.17	0.07	10.51	36.71	31.00	2.00	40.00	0.24	0.00	13.47	-2.97	10.50	12.94	-2.44	0.18
551.00	11152.00	166.05	0.00	1.64	13.00	0.08	1.17	0.07	10.51	36.71	31.00	2.00	40.00	0.24	12.33	9.96	-9.96	0.00	14.30	0.00	0.00
552.00	11152.00	178.52	0.00	1.64	13.00	0.08	1.17	0.07	10.51	36.71	31.00	2.00	40.00	0.24	12.47	9.43	-9.43	0.00	13.43	0.00	0.00
553.00	11152.00	185.88	7.36	1.79	0.00	0.09	1.28	0.07	10.41	36.86	31.00	2.00	41.00	0.24	0.00	11.71	-1.94	9.77	10.99	-1.22	0.39
554.00	11156.00	0.00	0.00	1.74	16.00	0.06	1.24	0.05	14.13	33.86	24.00	0.00	67.00	0.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00
555.00	11156.00	4.40	4.40	1.68	0.00	0.06	1.20	0.05	14.13	33.86	24.00	0.00	67.00	0.14	0.00	10.76	-4.62	6.14	7.90	-1.76	-0.68
556.00	11156.00	8.87	0.00	1.68	16.00	0.06	1.20	0.05	14.13	33.86	24.00	0.00	67.00	0.14	8.87	8.64	-8.64	0.00	9.16	0.00	0.00
557.00	11156.00	16.40	7.53	1.68	0.00	0.06	1.20	0.05	13.98	34.00	24.00	0.00	68.00	0.14	0.00	15.15	1.59	16.74	11.61	5.13	1.70
558.00	11156.00	17.47	8.60	1.68	0.00	0.06	1.20	0.05	13.98	34.00	24.00	0.00	68.00	0.14	0.00	14.37	-3.77	10.60	11.09	-0.49	0.08
559.00	11156.00	20.07	0.00	1.70	16.00	0.06	1.22	0.05	13.98	34.00	24.00	0.00	68.00	0.14	11.20	12.44	-12.44	0.00	13.70	0.00	0.00
560.00	11156.00	32.15	0.00	1.70	16.00	0.06	1.22	0.05	13.98	34.00	24.00	0.00	68.00	0.14	12.08	14.07	-14.07	0.00	15.98	0.00	0.00
561.00	11156.00	33.40	1.25	1.70	0.00	0.06	1.22	0.05	13.98	34.00	24.00	0.00	68.00	0.14	0.00	25.59	-2.89	22.70	19.69	3.01	0.73
562.00	11156.00	39.65	7.50	1.70	0.00	0.06	1.22	0.05	13.84	34.14	24.00	0.00	69.00	0.14	0.00	18.72	2.74	21.45	15.01	6.44	1.73
563.00	11156.00	43.33	11.18	1.69	0.00	0.06	1.21	0.05	13.84	34.14	24.00	0.00	69.00	0.14	0.00	15.66	-0.56	15.10	12.87	2.23	0.94
564.00	11156.00	44.65	12.50	1.69	0.00	0.06	1.21	0.05	13.84	34.14	24.00	0.00	69.00	0.14	0.00	14.66	-3.16	11.50	12.15	-0.65	0.24
565.00	11156.00	44.78	0.00	1.69	16.00	0.06	1.21	0.05	13.84	34.14	24.00	0.00	69.00	0.14	12.63	14.56	-14.56	0.00	16.94	0.00	0.00
566.00	11156.00	56.57	0.00	1.69	16.00	0.06	1.21	0.05	13.84	34.14	24.00	0.00	69.00	0.14	11.78	15.40	-15.40	0.00	18.08	0.00	0.00
567.00	11156.00	65.57	9.00	1.69	0.00	0.06	1.21	0.05	13.69	34.29	24.00	0.00	70.00	0.14	0.00	18.16	-7.66	10.50	15.04	-4.54	-0.55
568.00	11156.00	68.12	0.00	1.69	16.00	0.06	1.21	0.05	13.69	34.29	24.00	0.00	70.00	0.14	11.55	15.96	-15.96	0.00	18.86	0.00	0.00

569.00	11156.00	79.95	0.00	1.69	16.00	0.06	1.21	0.05	13.69	34.29	24.00	0.00	70.00	0.14	11.83	16.05	-16.05	0.00	19.09	0.00	0.00
570.00	11156.00	87.82	7.87	1.54	0.00	0.06	1.10	0.05	13.55	34.43	24.00	0.00	71.00	0.14	0.00	21.56	-9.86	11.70	17.91	-6.20	-0.68
571.00	11156.00	92.82	0.00	1.54	16.00	0.06	1.10	0.05	13.55	34.43	24.00	0.00	71.00	0.14	12.87	16.70	-16.70	0.00	20.11	0.00	0.00
572.00	11156.00	104.18	0.00	1.54	16.00	0.06	1.10	0.05	13.55	34.43	24.00	0.00	71.00	0.14	11.37	17.49	-17.49	0.00	20.95	0.00	0.00
573.00	11156.00	104.82	0.64	1.41	0.00	0.05	1.01	0.05	13.55	34.43	24.00	0.00	71.00	0.14	0.00	33.91	-14.91	19.00	26.91	-7.91	-0.67
574.00	11156.00	112.15	7.97	1.41	0.00	0.05	1.01	0.05	13.42	34.57	24.00	0.00	72.00	0.14	0.00	23.22	-11.87	11.35	19.37	-8.02	-0.88
575.00	11156.00	115.93	0.00	1.41	16.00	0.05	1.01	0.05	13.42	34.57	24.00	0.00	72.00	0.14	11.75	19.10	-19.10	0.00	22.93	0.00	0.00
576.00	11156.00	128.07	0.00	1.41	16.00	0.05	1.01	0.05	13.42	34.57	24.00	0.00	72.00	0.14	12.13	18.71	-18.71	0.00	22.55	0.00	0.00
577.00	11156.00	129.90	1.83	1.41	0.00	0.05	1.01	0.05	13.42	34.57	24.00	0.00	72.00	0.14	0.00	31.51	-11.81	19.70	25.28	-5.58	-0.39
578.00	11156.00	136.15	8.08	1.69	0.00	0.06	1.21	0.05	13.28	34.71	24.00	0.00	73.00	0.14	0.00	18.89	-8.90	9.99	15.82	-5.83	-0.71
579.00	11156.00	138.40	10.33	1.69	0.00	0.06	1.21	0.05	13.28	34.71	24.00	0.00	73.00	0.14	0.00	16.80	-3.70	13.10	14.29	-1.19	0.22
580.00	11156.00	140.30	0.00	1.69	16.00	0.06	1.21	0.05	13.28	34.71	24.00	0.00	73.00	0.14	12.23	15.21	-15.21	0.00	18.39	0.00	0.00
581.00	11156.00	152.75	0.00	1.69	16.00	0.06	1.21	0.05	13.28	34.71	24.00	0.00	73.00	0.14	12.45	14.85	-14.85	0.00	17.99	0.00	0.00
582.00	11156.00	164.40	0.00	1.69	16.00	0.06	1.21	0.05	13.14	34.86	24.00	0.00	74.00	0.14	11.65	15.19	-15.19	0.00	18.32	0.00	0.00
583.00	11156.00	176.60	0.00	1.69	16.00	0.06	1.21	0.05	13.14	34.86	24.00	0.00	74.00	0.14	12.20	14.94	-14.94	0.00	18.06	0.00	0.00
584.00	11156.00	188.08	0.00	1.69	16.00	0.06	1.21	0.05	13.01	35.00	24.00	0.00	75.00	0.14	11.48	15.28	-15.28	0.00	18.41	0.00	0.00
585.00	11156.00	200.02	0.00	1.69	16.00	0.06	1.21	0.05	13.01	35.00	24.00	0.00	75.00	0.14	11.93	15.10	-15.10	0.00	18.22	0.00	0.00
586.00	11156.00	207.90	7.88	1.69	0.00	0.07	1.21	0.05	12.88	35.14	24.00	0.00	76.00	0.14	0.00	18.55	-6.85	11.70	15.53	-3.83	-0.33

### Appendix 3: Piperacillin Final Model Control File and Output

```
$PROBLEM PIPERACILLIN PPK PREMATURE INFANTS - PPRU SCAVENGE SAMPLING
$INPUT ORDN ID DATE=DROP TIME EVID AMT AMTK=DROP DUR RATE DI DV SCAV GA GAGR PNA PMA BW CWT SEX RACE ETHN=DROP HISP
APGR SRCR2
$DATA pipnobld12h.csv IGNORE=#
$SUBROUTINES ADVAN1 TRANS2
$PK
IF (AMT.GT.0) THEN
TDOS=TIME
TAD=0.0
ENDIF
IF (AMT.EQ.0) TAD=TIME-TDOS
TVCL=THETA(1)*(CWT**0.75)*(0.5/SRCR2)
CL=TVCL*EXP(ETA(1))
TVV=THETA(2)*CWT
V=TVV*EXP(ETA(2))
K=CL/V
HFLF=0.693/K
S1=V
$ERROR
IPRED=F
Y=F+F*ERR(1)
IRES=DV-F
```



```

IWRES=IRES/IPRED
W=F

$THETA
(0.01, 0.7, 5)
(0.1, 3, 10)

$OMEGA BLOCK(2)
0.5 0.1
0.5

$SIGMA
(0.25)

$ESTIMATION MAXEVAL=9999 PRINT=5 SIGDIG=3 METHOD=1 INTERACTION NOABORT POSTHOC

$COV PRINT=E

$TABLE ORDN ID TIME TAD CWT AMT CL V K HFLF PMA GA GAGR PNA ETA1 ETA2 IPRED DI NOPRINT ONEHEADER FILE=80.tbl
$TABLE ID ETA1 ETA2 TIME IPRED WRES IWRES EVID NOPRINT ONEHEADER FILE=sdtab80
$TABLE ID CL V NOPRINT ONEHEADER FILE=patab80
$TABLE ID RACE SEX HISP NOPRINT ONEHEADER FILE=catab80
$TABLE ID GA PNA PMA CWT APGR SRCR2 NOPRINT ONEHEADER FILE=cotab80

NM-TRAN MESSAGES

WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1

(WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.
CREATING MUMODEL ROUTINE...
FSUBS
FSUBS_MU.F90
1 file(s) copied.

```

License Registered to: Duke Clinical Research Institute

Expiration Date: 14 MAR 2012

Current Date: 14 JUL 2011

Days until program expires : 245

1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.1.0

ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, 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

PIPERACILLIN PPK PREMATURE INFANTS - PPRU SCAVENGE SAMPLING

ODATA CHECKOUT RUN: NO

DATA SET LOCATED ON UNIT NO.: 2

THIS UNIT TO BE REWOUND: NO

NO. OF DATA RECS IN DATA SET: 1041

NO. OF DATA ITEMS IN DATA SET: 22

ID DATA ITEM IS DATA ITEM NO.: 2

DEP VARIABLE IS DATA ITEM NO.: 9

MDV DATA ITEM IS DATA ITEM NO.: 22

0INDICES PASSED TO SUBROUTINE PRED:

4 3 5 7 0 0 0 0

0 0

0LABELS FOR DATA ITEMS:

ORDN ID TIME EVID AMT DUR RATE DI DV SCAV GA GAGR PNA PMA BW CWT SEX RACE HISP APGR SRCR2 MDV

0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:

TAD CL V K HFLF IPRE IWRE

0FORMAT FOR DATA:

(3(6E11.0/),3E11.0,1F2.0)

TOT. NO. OF OBS RECS: 211

TOT. NO. OF INDIVIDUALS: 56

OLENGTH OF THETA: 2  
 ODEFAULT THETA BOUNDARY TEST OMITTED: NO  
 OOMEGA HAS BLOCK FORM:  
   1  
   1 1  
 ODEFAULT OMEGA BOUNDARY TEST OMITTED: NO  
 OSIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1  
 ODEFAULT SIGMA BOUNDARY TEST OMITTED: NO  
 OINITIAL ESTIMATE OF THETA:  
 LOWER BOUND INITIAL EST UPPER BOUND  
   0.1000E-01 0.7000E+00 0.5000E+01  
   0.1000E+00 0.3000E+01 0.1000E+02  
 OINITIAL ESTIMATE OF OMEGA:  
 BLOCK SET NO. BLOCK NO FIXED  
   1 NO  
   0.5000E+00  
   0.1000E+00 0.5000E+00  
 OINITIAL ESTIMATE OF SIGMA:  
   0.2500E+00  
 OESTIMATION STEP OMITTED: NO  
 OCONDITIONAL ESTIMATES USED: YES  
 OCENTERED ETA: NO  
 OEPS-ETA INTERACTION: YES  
 OLAPLACIAN OBJ. FUNC.: NO  
 ONO. OF FUNCT. EVALS. ALLOWED: 9999  
 ONO. OF SIG. FIGURES REQUIRED: 3  
 OINTERMEDIATE PRINTOUT: YES  
 OESTIMATE OUTPUT TO MSF: NO  
 OABORT WITH PRED EXIT CODE 1: NO  
 OIND. OBJ. FUNC. VALUES SORTED: NO  
 OCOVARIANCE STEP OMITTED: NO  
 OEIGENVLS. PRINTED: YES  
 OSPECIAL COMPUTATION: NO

COMPRESSED FORMAT: NO  
 0 TABLES OMITTED: NO  
 NO. OF TABLES: 5  
 0-- TABLE 1 --  
 PRINTED: NO  
 HEADERS: ONE  
 FILE TO BE FORWARDED: NO  
 0 USER-CHOSEN ITEMS:  
 ORDN ID TIME TAD CWT AMT CL V K HFLF PMA GA GAGR PNA ETA1 ETA2 IPRED DI  
 0-- TABLE 2 --  
 PRINTED: NO  
 HEADERS: ONE  
 FILE TO BE FORWARDED: NO  
 0 USER-CHOSEN ITEMS:  
 ID ETA1 ETA2 TIME IPRED IWRES EVID  
 0-- TABLE 3 --  
 PRINTED: NO  
 HEADERS: ONE  
 FILE TO BE FORWARDED: NO  
 0 USER-CHOSEN ITEMS:  
 ID CL V  
 0-- TABLE 4 --  
 PRINTED: NO  
 HEADERS: ONE  
 FILE TO BE FORWARDED: NO  
 0 USER-CHOSEN ITEMS:  
 ID RACE SEX HISP  
 0-- TABLE 5 --  
 PRINTED: NO  
 HEADERS: ONE  
 FILE TO BE FORWARDED: NO  
 0 USER-CHOSEN ITEMS:  
 ID GA PNA PMA CWT APGR SRCR2

THE FOLLOWING LABELS ARE EQUIVALENT

PRED=PREDI

RES=RESI

WRES=WRESI

1 DOUBLE PRECISION PREDPP VERSION 7.1.0

ONE COMPARTMENT MODEL (ADVAN1)

0 MAXIMUM NO. OF BASIC PK PARAMETERS: 2

0 BASIC PK PARAMETERS (AFTER TRANSLATION):

ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1

TRANSLATOR WILL CONVERT PARAMETERS

CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)

0 COMPARTMENT ATTRIBUTES

COMPT. NO. FUNCTION INITIAL ON/OFF DOSE DEFAULT DEFAULT  
STATUS ALLOWED FOR DOSE FOR OBS.

1 CENTRAL ON NO YES YES YES

2 OUTPUT OFF YES NO NO NO

1

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG

COMPT. NO.

INDICES

SCALE BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB

FRACTION RATE DURATION LAG

1 3 \* \* \* \* \*

2 \* - - - - -

- PARAMETER IS NOT ALLOWED FOR THIS MODEL

\* PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;

WILL DEFAULT TO ONE IF APPLICABLE

0 DATA ITEM INDICES USED BY PRED ARE:

EVENT ID DATA ITEM IS DATA ITEM NO.: 4

TIME DATA ITEM IS DATA ITEM NO.: 3

DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 5

DOSE RATE DATA ITEM IS DATA ITEM NO.: 7

OPK SUBROUTINE CALLED WITH EVERY EVENT RECORD.  
PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.  
ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.

1

#METH: First Order Conditional Estimation with Interaction  
MONITORING OF SEARCH:

ITERATION NO.:	0	OBJECTIVE VALUE:	1724.98363881194	NO. OF FUNC. EVALS.:	5
CUMULATIVE NO. OF FUNC. EVALS.:	5				
PARAMETER:	1.0000E-01	1.0000E-01	1.0000E-01	1.0000E-01	1.0000E-01
GRADIENT:	8.2461E+01	1.2513E+01	-9.1917E+01	-1.4604E+02	-1.7424E+01
ITERATION NO.:	5	OBJECTIVE VALUE:	1622.58025834205	NO. OF FUNC. EVALS.:	7
CUMULATIVE NO. OF FUNC. EVALS.:	36				
PARAMETER:	-4.5075E-01	1.8097E-01	5.0652E-01	9.2214E-01	-2.3055E-01
GRADIENT:	-2.2016E+01	8.9960E+00	3.4526E+01	-1.1554E+01	1.1767E+00
ITERATION NO.:	10	OBJECTIVE VALUE:	1618.17222480341	NO. OF FUNC. EVALS.:	6
CUMULATIVE NO. OF FUNC. EVALS.:	67				
PARAMETER:	-3.4273E-01	3.9188E-02	3.5714E-01	7.9126E-01	-4.3053E-01
GRADIENT:	3.6953E-01	-2.4198E-01	-7.3649E-01	6.2884E-01	-1.5543E-01
ITERATION NO.:	15	OBJECTIVE VALUE:	1618.16848422040	NO. OF FUNC. EVALS.:	11
CUMULATIVE NO. OF FUNC. EVALS.:	105				
PARAMETER:	-3.3725E-01	5.4531E-02	3.5818E-01	7.9155E-01	-4.2066E-01
GRADIENT:	-6.0120E-02	-1.7027E-02	-2.1010E-02	1.0720E-02	1.1909E-02
ITERATION NO.:	17	OBJECTIVE VALUE:	1618.16842662264	NO. OF FUNC. EVALS.:	6
CUMULATIVE NO. OF FUNC. EVALS.:	120				
PARAMETER:	-3.3615E-01	5.6676E-02	3.5829E-01	7.9169E-01	-4.2068E-01
GRADIENT:	3.7867E-03	-2.4240E-03	-2.9379E-03	-8.7965E-04	2.9268E-03

Elapsed estimation time in seconds: 3.80

#TERM:  
MINIMIZATION SUCCESSFUL  
NO. OF FUNCTION EVALUATIONS USED: 120  
NO. OF SIG. DIGITS IN FINAL EST.: 3.2

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: -1.7434E-03 -5.1293E-03  
SE: 1.1373E-01 1.4037E-01

P VAL.: 9.8777E-01 9.7085E-01

ETAsrink(%): 6.1921E+00 1.1147E+01  
EPSsrink(%): 6.8997E+00

#ITERE:  
Elapsed covariance time in seconds: 2.73

### Appendix 4: Piperacillin PK Dataset

TABLE NO. 1

ORDN	ID	TIME	TAD	CWLT	AMT	CL	V	K	HFLF	PMA	GA	GAGR	PNA	ETA1	ETA2	IPRED	DI	DV	PRED	RES	WRES
1.00	71.00	0.00	0.00	1.36	138.00	1.61	17.98	0.09	7.73	34.71	31.00	2.00	23.00	1.15	1.52	0.00	0.00	0.00	0.00	0.00	0.00
2.00	71.00	8.00	0.00	1.36	138.00	1.61	17.98	0.09	7.73	34.86	31.00	2.00	24.00	1.15	1.52	3.83	8.00	0.00	12.84	0.00	0.00
3.00	71.00	11.00	3.00	1.37	0.00	1.62	18.08	0.09	7.74	34.86	31.00	2.00	24.00	1.15	1.52	8.88	0.00	7.57	33.02	-25.45	-0.53
4.00	73.00	0.00	0.00	0.79	83.00	0.17	2.98	0.06	11.89	26.14	25.00	0.00	3.00	-0.18	0.26	0.00	0.00	0.00	0.00	0.00	0.00
5.00	73.00	1.42	1.42	0.79	0.00	0.17	2.98	0.06	11.89	26.14	25.00	0.00	3.00	-0.18	0.26	26.03	0.00	0.15	32.48	-32.33	-0.60
6.00	73.00	11.17	11.17	0.79	0.00	0.17	2.98	0.06	11.89	26.29	25.00	0.00	4.00	-0.18	0.26	14.74	0.00	0.15	13.51	-13.36	-0.79
7.00	73.00	12.17	0.00	0.79	83.00	0.20	2.98	0.07	10.29	26.29	25.00	0.00	4.00	-0.18	0.26	13.78	12.17	0.00	12.18	0.00	0.00
8.00	73.00	13.17	1.00	0.78	0.00	0.18	2.94	0.06	11.60	26.29	25.00	0.00	4.00	-0.18	0.26	40.14	0.00	27.80	45.36	-17.56	-0.12
9.00	73.00	20.42	8.25	0.77	0.00	0.17	2.90	0.06	11.57	26.29	25.00	0.00	4.00	-0.18	0.26	26.34	0.00	0.15	23.51	-23.36	-0.80
10.00	73.00	23.83	11.66	0.77	0.00	0.17	2.90	0.06	11.57	26.29	25.00	0.00	4.00	-0.18	0.26	21.47	0.00	59.90	17.15	42.75	2.70
11.00	73.00	24.17	0.00	0.77	83.00	0.17	2.90	0.06	11.57	26.29	25.00	0.00	4.00	-0.18	0.26	21.04	12.00	0.00	16.62	0.00	0.00
12.00	73.00	28.42	4.25	0.77	0.00	0.17	2.90	0.06	11.57	26.29	25.00	0.00	4.00	-0.18	0.26	38.81	0.00	18.40	36.80	-18.40	-0.28
13.00	73.00	36.17	0.00	0.79	83.00	0.13	2.98	0.04	16.05	26.43	25.00	0.00	5.00	-0.18	0.26	27.07	12.00	0.00	21.41	0.00	0.00
15.00	73.00	48.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.43	25.00	0.00	5.00	-0.18	0.26	35.89	12.00	0.00	28.30	0.00	0.00
16.00	73.00	60.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.57	25.00	0.00	6.00	-0.18	0.26	39.40	12.00	0.00	30.34	0.00	0.00
17.00	73.00	72.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.57	25.00	0.00	6.00	-0.18	0.26	41.47	12.00	0.00	31.25	0.00	0.00
18.00	73.00	84.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.71	25.00	0.00	7.00	-0.18	0.26	42.69	12.00	0.00	31.64	0.00	0.00
19.00	73.00	96.67	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.71	25.00	0.00	7.00	-0.18	0.26	42.45	12.50	0.00	30.75	0.00	0.00
20.00	73.00	108.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.86	25.00	0.00	8.00	-0.18	0.26	44.23	11.50	0.00	32.52	0.00	0.00
21.00	73.00	120.67	0.00	0.72	83.00	0.12	2.70	0.04	15.66	26.86	25.00	0.00	8.00	-0.18	0.26	43.34	12.50	0.00	31.12	0.00	0.00
22.00	73.00	132.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	27.00	25.00	0.00	9.00	-0.18	0.26	44.76	11.50	0.00	32.69	0.00	0.00
23.00	73.00	144.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	27.00	25.00	0.00	9.00	-0.18	0.26	44.62	12.00	0.00	32.28	0.00	0.00
24.00	73.00	156.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	27.14	25.00	0.00	10.00	-0.18	0.26	44.54	12.00	0.00	32.10	0.00	0.00
25.00	73.00	168.67	0.00	0.72	83.00	0.12	2.70	0.04	15.66	27.14	25.00	0.00	10.00	-0.18	0.26	43.52	12.50	0.00	30.94	0.00	0.00
26.00	73.00	180.17	0.00	0.72	83.00	0.12	2.70	0.04	15.66	27.29	25.00	0.00	11.00	-0.18	0.26	44.87	11.50	0.00	32.60	0.00	0.00
27.00	73.00	181.00	0.83	0.72	0.00	0.12	2.70	0.04	15.66	27.29	25.00	0.00	11.00	-0.18	0.26	73.26	0.00	42.80	69.13	-26.33	-0.18
28.00	74.00	0.00	0.00	0.78	68.00	0.26	8.90	0.03	23.30	26.71	24.00	0.00	17.00	1.15	1.37	0.00	0.00	0.00	0.00	0.00	0.00
29.00	74.00	12.00	0.00	0.85	68.00	0.28	9.76	0.03	23.84	26.86	24.00	0.00	18.00	1.15	1.37	4.95	12.00	0.00	17.93	0.00	0.00



30.00	74.00	24.00	0.00	0.88	68.00	0.29	10.11	0.03	24.05	26.86	24.00	0.00	18.00	1.15	1.37	8.18	12.00	0.00	28.64	0.00	0.00
31.00	74.00	36.00	0.00	0.83	68.00	0.28	9.53	0.03	23.70	27.00	24.00	0.00	19.00	1.15	1.37	11.16	12.00	0.00	37.91	0.00	0.00
32.00	74.00	47.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.00	24.00	0.00	19.00	1.15	1.37	12.43	11.50	0.00	41.34	0.00	0.00
33.00	74.00	59.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.14	24.00	0.00	20.00	1.15	1.37	13.59	12.00	0.00	44.23	0.00	0.00
34.00	74.00	71.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.14	24.00	0.00	20.00	1.15	1.37	14.41	12.00	0.00	46.11	0.00	0.00
35.00	74.00	83.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.29	24.00	0.00	21.00	1.15	1.37	14.99	12.00	0.00	47.33	0.00	0.00
36.00	74.00	92.00	8.50	0.88	0.00	0.29	10.11	0.03	24.05	27.29	24.00	0.00	21.00	1.15	1.37	17.04	0.00	20.30	54.58	-34.28	-0.22
37.00	74.00	95.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.29	24.00	0.00	21.00	1.15	1.37	15.41	12.00	0.00	48.12	0.00	0.00
38.00	74.00	108.00	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.43	24.00	0.00	22.00	1.15	1.37	15.47	12.50	0.00	47.76	0.00	0.00
39.00	74.00	119.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.43	24.00	0.00	22.00	1.15	1.37	15.97	11.50	0.00	49.28	0.00	0.00
40.00	74.00	132.00	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.57	24.00	0.00	23.00	1.15	1.37	15.87	12.50	0.00	48.51	0.00	0.00
41.00	74.00	137.25	5.25	0.88	0.00	0.29	10.11	0.03	24.05	27.57	24.00	0.00	23.00	1.15	1.37	19.47	0.00	41.70	62.32	-20.62	0.06
42.00	74.00	143.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.57	24.00	0.00	23.00	1.15	1.37	16.26	11.50	0.00	49.77	0.00	0.00
43.00	74.00	156.08	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.71	24.00	0.00	24.00	1.15	1.37	16.03	12.58	0.00	48.68	0.00	0.00
44.00	74.00	161.00	4.92	0.88	0.00	0.29	10.11	0.03	24.05	27.71	24.00	0.00	24.00	1.15	1.37	19.79	0.00	10.30	63.21	-52.91	-0.44
45.00	74.00	168.00	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.71	24.00	0.00	24.00	1.15	1.37	16.18	11.92	0.00	49.14	0.00	0.00
46.00	74.00	179.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.86	24.00	0.00	25.00	1.15	1.37	16.48	11.50	0.00	50.19	0.00	0.00
47.00	74.00	187.00	7.50	0.88	0.00	0.29	10.11	0.03	24.05	27.86	24.00	0.00	25.00	1.15	1.37	18.74	0.00	7.07	58.76	-51.69	-0.49
48.00	74.00	191.50	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.86	24.00	0.00	25.00	1.15	1.37	16.46	12.00	0.00	49.98	0.00	0.00
49.00	74.00	203.25	0.00	0.88	68.00	0.29	10.11	0.03	24.05	27.86	24.00	0.00	25.00	1.15	1.37	16.56	11.75	0.00	50.29	0.00	0.00
50.00	74.00	211.00	7.75	0.88	0.00	0.29	10.11	0.03	24.05	28.00	24.00	0.00	26.00	1.15	1.37	18.67	0.00	7.22	58.31	-51.09	-0.48
51.00	78.00	0.00	0.00	0.58	85.00	0.74	5.40	0.14	5.08	28.00	24.00	0.00	22.00	1.02	1.16	0.00	0.00	0.00	0.00	0.00	0.00
52.00	78.00	5.17	5.17	0.58	0.00	0.74	5.40	0.14	5.08	28.00	24.00	0.00	22.00	1.02	1.16	8.05	0.00	11.50	23.24	-11.74	-0.26
53.00	78.00	12.00	0.00	0.58	85.00	0.74	5.40	0.14	5.08	28.00	24.00	0.00	22.00	1.02	1.16	3.17	12.00	0.00	7.95	0.00	0.00
54.00	78.00	20.00	8.00	0.58	0.00	0.74	5.40	0.14	5.08	28.00	24.00	0.00	22.00	1.02	1.16	6.54	0.00	3.58	17.16	-13.58	-0.57
87.00	117.00	0.00	0.00	1.21	92.00	0.15	0.59	0.26	2.69	32.00	24.00	0.00	53.00	-1.81	-1.79	0.00	0.00	0.00	0.00	0.00	0.00
88.00	117.00	8.37	0.00	1.22	92.00	0.15	0.59	0.26	2.69	32.14	24.00	0.00	54.00	-1.81	-1.79	19.31	8.37	0.00	3.12	0.00	0.00
89.00	117.00	16.00	0.00	1.32	92.00	0.16	0.64	0.25	2.74	32.14	24.00	0.00	54.00	-1.81	-1.79	25.04	7.63	0.00	4.04	0.00	0.00
90.00	117.00	24.42	8.42	1.40	0.00	0.17	0.68	0.25	2.79	32.14	24.00	0.00	54.00	-1.81	-1.79	20.72	0.00	29.50	3.34	26.17	3.63
91.00	117.00	24.70	0.00	1.58	92.00	0.18	0.76	0.24	2.87	32.14	24.00	0.00	54.00	-1.81	-1.79	17.16	8.70	0.00	2.76	0.00	0.00

92.00	117.00	32.95	0.00	1.64	92.00	0.19	0.79	0.24	2.90	32.29	24.00	0.00	55.00	-1.81	-1.79	19.44	8.25	0.00	3.14	0.00	0.00
93.00	117.00	36.78	3.83	1.64	0.00	0.19	0.79	0.24	2.90	32.29	24.00	0.00	55.00	-1.81	-1.79	57.07	0.00	9.02	9.34	-0.32	-3.98
94.00	117.00	40.20	0.00	1.68	92.00	0.19	0.81	0.24	2.92	32.29	24.00	0.00	55.00	-1.81	-1.79	24.79	7.25	0.00	4.01	0.00	0.00
95.00	117.00	48.70	0.00	1.71	92.00	0.15	0.83	0.18	3.90	32.29	24.00	0.00	55.00	-1.81	-1.79	31.17	8.50	0.00	5.05	0.00	0.00
96.00	117.00	56.20	0.00	1.71	92.00	0.08	0.83	0.10	6.83	32.43	24.00	0.00	56.00	-1.81	-1.79	68.00	7.50	0.00	11.13	0.00	0.00
97.00	117.00	61.25	5.05	1.71	0.00	0.12	0.83	0.14	4.88	32.43	24.00	0.00	56.00	-1.81	-1.79	89.59	0.00	240.50	14.67	225.83	11.95
98.00	117.00	64.37	0.00	1.71	92.00	0.12	0.83	0.14	4.88	32.43	24.00	0.00	56.00	-1.81	-1.79	57.53	8.17	0.00	9.36	0.00	0.00
99.00	117.00	72.20	0.00	1.71	92.00	0.10	0.83	0.12	5.86	32.43	24.00	0.00	56.00	-1.81	-1.79	68.24	7.83	0.00	11.12	0.00	0.00
100.00	117.00	79.70	0.00	1.71	92.00	0.08	0.83	0.10	6.83	32.43	24.00	0.00	56.00	-1.81	-1.79	85.33	7.50	0.00	13.94	0.00	0.00
101.00	117.00	88.53	0.00	1.71	92.00	0.07	0.83	0.09	7.81	32.57	24.00	0.00	57.00	-1.81	-1.79	91.03	8.83	0.00	14.86	0.00	0.00
102.00	117.00	96.20	0.00	2.46	92.00	0.11	1.19	0.09	7.48	32.57	24.00	0.00	57.00	-1.81	-1.79	70.03	7.67	0.00	11.44	0.00	0.00
103.00	117.00	104.20	0.00	2.46	92.00	0.11	1.19	0.09	7.48	32.71	24.00	0.00	58.00	-1.81	-1.79	71.16	8.00	0.00	11.62	0.00	0.00
104.00	117.00	107.27	3.07	2.46	0.00	0.13	1.19	0.11	6.42	32.71	24.00	0.00	58.00	-1.81	-1.79	108.17	0.00	83.00	17.75	65.25	0.22
105.00	117.00	111.87	0.00	2.46	92.00	0.15	1.19	0.13	5.35	32.71	24.00	0.00	58.00	-1.81	-1.79	59.59	7.67	0.00	9.70	0.00	0.00
106.00	117.00	121.02	0.00	2.46	92.00	0.19	1.19	0.16	4.28	32.71	24.00	0.00	58.00	-1.81	-1.79	31.84	9.15	0.00	5.14	0.00	0.00
107.00	117.00	128.20	0.00	2.36	92.00	0.15	1.14	0.13	5.29	32.86	24.00	0.00	59.00	-1.81	-1.79	45.45	7.18	0.00	7.40	0.00	0.00
108.00	117.00	130.55	2.35	2.36	0.00	0.15	1.14	0.13	5.29	32.86	24.00	0.00	59.00	-1.81	-1.79	94.60	0.00	91.80	15.55	76.25	1.29
109.00	117.00	137.03	0.00	2.36	92.00	0.15	1.14	0.13	5.29	32.86	24.00	0.00	59.00	-1.81	-1.79	40.50	8.83	0.00	6.58	0.00	0.00
110.00	117.00	144.20	0.00	2.36	92.00	0.15	1.14	0.13	5.29	32.86	24.00	0.00	59.00	-1.81	-1.79	48.40	7.17	0.00	7.88	0.00	0.00
111.00	117.00	152.28	0.00	2.36	92.00	0.15	1.14	0.13	5.29	33.00	24.00	0.00	60.00	-1.81	-1.79	45.78	8.08	0.00	7.45	0.00	0.00
112.00	117.00	160.28	0.00	2.36	92.00	0.15	1.14	0.13	5.29	33.00	24.00	0.00	60.00	-1.81	-1.79	45.30	8.00	0.00	7.37	0.00	0.00
113.00	117.00	167.70	0.00	2.28	92.00	0.15	1.10	0.13	5.25	33.00	24.00	0.00	60.00	-1.81	-1.79	49.91	7.42	0.00	8.13	0.00	0.00
114.00	117.00	176.22	0.00	2.28	92.00	0.18	1.10	0.17	4.20	33.14	24.00	0.00	61.00	-1.81	-1.79	33.53	8.52	0.00	5.43	0.00	0.00
115.00	117.00	180.45	4.23	2.38	0.00	0.15	1.15	0.13	5.30	33.14	24.00	0.00	61.00	-1.81	-1.79	66.09	0.00	34.00	10.83	23.17	-1.68
116.00	117.00	184.20	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.14	24.00	0.00	61.00	-1.81	-1.79	40.48	7.98	0.00	6.59	0.00	0.00
117.00	117.00	185.20	1.00	2.38	0.00	0.15	1.15	0.13	5.30	33.14	24.00	0.00	61.00	-1.81	-1.79	108.08	0.00	8.00	17.82	-9.82	-3.88
118.00	117.00	192.20	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.14	24.00	0.00	61.00	-1.81	-1.79	43.29	8.00	0.00	7.05	0.00	0.00
119.00	117.00	200.53	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.29	24.00	0.00	62.00	-1.81	-1.79	42.41	8.33	0.00	6.90	0.00	0.00
121.00	117.00	208.87	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.29	24.00	0.00	62.00	-1.81	-1.79	42.06	8.33	0.00	6.84	0.00	0.00
122.00	117.00	218.03	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.29	24.00	0.00	62.00	-1.81	-1.79	37.68	9.17	0.00	6.12	0.00	0.00

123.00	117.00	224.53	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.43	24.00	0.00	63.00	-1.81	-1.79	51.47	6.50	0.00	8.40	0.00	0.00
124.00	117.00	232.53	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.43	24.00	0.00	63.00	-1.81	-1.79	47.16	8.00	0.00	7.67	0.00	0.00
125.00	117.00	239.95	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.43	24.00	0.00	63.00	-1.81	-1.79	49.23	7.42	0.00	8.02	0.00	0.00
126.00	117.00	248.53	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.57	24.00	0.00	64.00	-1.81	-1.79	42.98	8.58	0.00	6.98	0.00	0.00
127.00	117.00	254.20	5.67	2.38	0.00	0.15	1.15	0.13	5.30	33.57	24.00	0.00	64.00	-1.81	-1.79	59.90	0.00	107.00	9.78	97.22	6.25
128.00	117.00	256.20	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.57	24.00	0.00	64.00	-1.81	-1.79	46.12	7.67	0.00	7.50	0.00	0.00
129.00	117.00	264.70	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.57	24.00	0.00	64.00	-1.81	-1.79	42.41	8.50	0.00	6.89	0.00	0.00
130.00	117.00	272.12	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.57	24.00	0.00	64.00	-1.81	-1.79	47.43	7.42	0.00	7.72	0.00	0.00
131.00	117.00	276.20	4.08	2.38	0.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	76.34	0.00	37.00	12.51	24.49	-1.76
132.00	117.00	278.20	6.08	2.38	0.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	58.78	0.00	9.22	9.60	-0.38	-3.99
133.00	117.00	280.42	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	43.98	8.30	0.00	7.15	0.00	0.00
134.00	117.00	285.50	5.08	2.38	0.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	65.21	0.00	0.15	10.66	-10.51	-4.87
135.00	117.00	288.20	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	45.82	7.78	0.00	7.46	0.00	0.00
136.00	117.00	289.28	1.08	2.38	0.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	111.59	0.00	127.00	18.38	108.62	2.34
137.00	117.00	294.27	6.07	2.38	0.00	0.15	1.15	0.13	5.30	33.71	24.00	0.00	65.00	-1.81	-1.79	58.13	0.00	97.80	9.49	88.31	5.61
138.00	117.00	297.20	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	39.64	9.00	0.00	6.44	0.00	0.00
139.00	117.00	301.20	4.00	2.38	0.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	72.52	0.00	56.90	11.88	45.02	0.04
140.00	117.00	304.93	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	44.54	7.73	0.00	7.25	0.00	0.00
141.00	117.00	309.78	4.85	2.38	0.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	67.50	0.00	59.20	11.04	48.16	0.59
142.00	117.00	311.53	6.60	2.38	0.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	53.70	0.00	57.80	8.76	49.04	1.76
143.00	117.00	312.82	0.00	2.38	92.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	45.37	7.88	0.00	7.38	0.00	0.00
144.00	117.00	318.20	5.38	2.38	0.00	0.15	1.15	0.13	5.30	33.86	24.00	0.00	66.00	-1.81	-1.79	63.39	0.00	16.80	10.36	6.44	-3.26
145.00	117.00	320.37	0.00	2.38	92.00	0.15	1.15	0.13	5.30	34.00	24.00	0.00	67.00	-1.81	-1.79	47.74	7.55	0.00	7.77	0.00	0.00
146.00	117.00	325.70	5.33	2.38	0.00	0.15	1.15	0.13	5.30	34.00	24.00	0.00	67.00	-1.81	-1.79	64.99	0.00	208.00	10.62	197.38	15.09
147.00	117.00	328.65	0.00	2.38	92.00	0.15	1.15	0.13	5.30	34.00	24.00	0.00	67.00	-1.81	-1.79	44.20	8.28	0.00	7.19	0.00	0.00
148.00	117.00	332.45	3.80	2.38	0.00	0.15	1.15	0.13	5.30	34.00	24.00	0.00	67.00	-1.81	-1.79	77.22	0.00	78.80	12.66	66.15	1.52
149.00	117.00	336.60	0.00	2.38	92.00	0.15	1.15	0.13	5.30	34.00	24.00	0.00	67.00	-1.81	-1.79	44.89	7.95	0.00	7.30	0.00	0.00
150.00	117.00	337.70	1.10	2.38	0.00	0.15	1.15	0.13	5.30	34.00	24.00	0.00	67.00	-1.81	-1.79	110.50	0.00	98.30	18.20	80.10	0.88
151.00	117.00	345.63	9.03	2.38	0.00	0.15	1.15	0.13	5.30	34.14	24.00	0.00	68.00	-1.81	-1.79	39.20	0.00	14.20	6.36	7.84	-2.93
152.00	117.00	348.18	11.58	2.38	0.00	0.15	1.15	0.13	5.30	34.14	24.00	0.00	68.00	-1.81	-1.79	28.09	0.00	35.40	4.54	30.86	2.73

153.00	211.00	0.00	0.00	0.48	40.00	0.29	4.39	0.07	10.52	24.29	22.00	0.00	10.00	0.83	1.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
154.00	211.00	9.33	9.33	0.48	0.00	0.29	4.39	0.07	10.52	24.29	22.00	0.00	10.00	0.83	1.14	5.02	0.00	3.34	12.66	-9.32	-0.30		
155.00	211.00	13.47	0.00	0.48	40.00	0.40	4.39	0.09	7.65	24.43	22.00	0.00	11.00	0.83	1.14	3.45	13.47	0.00	7.59	0.00	0.00	0.00	0.00
156.00	211.00	17.47	4.00	0.48	0.00	0.40	4.39	0.09	7.65	24.43	22.00	0.00	11.00	0.83	1.14	8.90	0.00	0.15	22.64	-22.49	-0.59		
157.00	211.00	21.47	0.00	0.48	40.00	0.35	4.39	0.08	8.61	24.43	22.00	0.00	11.00	0.83	1.14	6.45	8.00	0.00	14.60	0.00	0.00	0.00	0.00
158.00	211.00	29.47	0.00	0.48	40.00	0.35	4.39	0.08	8.61	24.43	22.00	0.00	11.00	0.83	1.14	8.27	8.00	0.00	18.29	0.00	0.00	0.00	0.00
159.00	211.00	37.80	0.00	0.48	40.00	0.40	4.39	0.09	7.65	24.57	22.00	0.00	12.00	0.83	1.14	8.28	8.33	0.00	17.09	0.00	0.00	0.00	0.00
160.00	211.00	41.47	3.67	0.46	0.00	0.38	4.20	0.09	7.57	24.57	22.00	0.00	12.00	0.83	1.14	13.14	0.00	11.10	30.76	-19.66	-0.31		
161.00	211.00	46.20	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.57	22.00	0.00	12.00	0.83	1.14	6.64	8.40	0.00	12.68	0.00	0.00	0.00	0.00
162.00	211.00	53.47	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.57	22.00	0.00	12.00	0.83	1.14	6.48	7.27	0.00	12.43	0.00	0.00	0.00	0.00
163.00	211.00	59.73	6.26	0.52	0.00	0.56	4.75	0.12	5.86	24.57	22.00	0.00	12.00	0.83	1.14	7.22	0.00	12.50	14.54	-2.04	0.22		
164.00	211.00	62.47	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.71	22.00	0.00	13.00	0.83	1.14	5.22	9.00	0.00	9.34	0.00	0.00	0.00	0.00
165.00	211.00	65.47	3.00	0.52	0.00	0.56	4.75	0.12	5.86	24.71	22.00	0.00	13.00	0.83	1.14	9.74	0.00	21.60	22.71	-1.11	0.31		
166.00	211.00	69.47	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.71	22.00	0.00	13.00	0.83	1.14	6.07	7.00	0.00	11.91	0.00	0.00	0.00	0.00
167.00	211.00	77.47	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.71	22.00	0.00	13.00	0.83	1.14	5.72	8.00	0.00	10.83	0.00	0.00	0.00	0.00
169.00	211.00	85.47	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.86	22.00	0.00	14.00	0.83	1.14	5.58	8.00	0.00	10.54	0.00	0.00	0.00	0.00
170.00	211.00	93.88	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.86	22.00	0.00	14.00	0.83	1.14	5.27	8.42	0.00	9.79	0.00	0.00	0.00	0.00
171.00	211.00	101.47	7.59	0.52	0.00	0.56	4.75	0.12	5.86	24.86	22.00	0.00	14.00	0.83	1.14	5.68	0.00	4.00	10.95	-6.95	-0.29		
172.00	211.00	101.80	0.00	0.52	40.00	0.56	4.75	0.12	5.86	24.86	22.00	0.00	14.00	0.83	1.14	5.46	7.92	0.00	10.39	0.00	0.00	0.00	0.00
173.00	211.00	109.47	0.00	0.52	40.00	0.56	4.75	0.12	5.86	25.00	22.00	0.00	15.00	0.83	1.14	5.70	7.67	0.00	10.99	0.00	0.00	0.00	0.00
174.00	211.00	113.47	4.00	0.52	0.00	0.56	4.75	0.12	5.86	25.00	22.00	0.00	15.00	0.83	1.14	8.95	0.00	0.19	20.18	-19.99	-0.63		
218.00	259.00	0.00	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.14	24.00	0.00	50.00	-0.51	-0.52	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
219.00	259.00	7.58	0.00	1.08	47.00	0.51	1.87	0.27	2.54	31.14	24.00	0.00	50.00	-0.51	-0.52	3.42	7.58	0.00	2.08	0.00	0.00	0.00	0.00
220.00	259.00	15.33	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.29	24.00	0.00	51.00	-0.51	-0.52	3.65	7.75	0.00	2.23	0.00	0.00	0.00	0.00
221.00	259.00	23.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.29	24.00	0.00	51.00	-0.51	-0.52	3.36	8.08	0.00	2.06	0.00	0.00	0.00	0.00
222.00	259.00	31.58	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.29	24.00	0.00	51.00	-0.51	-0.52	3.27	8.17	0.00	2.00	0.00	0.00	0.00	0.00
223.00	259.00	39.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.43	24.00	0.00	52.00	-0.51	-0.52	3.55	7.83	0.00	2.17	0.00	0.00	0.00	0.00
224.00	259.00	47.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.43	24.00	0.00	52.00	-0.51	-0.52	3.43	8.00	0.00	2.10	0.00	0.00	0.00	0.00
225.00	259.00	55.92	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.43	24.00	0.00	52.00	-0.51	-0.52	2.98	8.50	0.00	1.83	0.00	0.00	0.00	0.00
226.00	259.00	62.92	7.00	1.10	0.00	0.52	1.90	0.27	2.56	31.57	24.00	0.00	53.00	-0.51	-0.52	4.42	0.00	6.38	2.69	3.69	0.78		

227.00	259.00	63.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.57	24.00	0.00	53.00	-0.51	-0.52	3.86	7.50	0.00	2.35	0.00	0.00
228.00	259.00	71.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.57	24.00	0.00	53.00	-0.51	-0.52	3.47	8.00	0.00	2.12	0.00	0.00
229.00	259.00	79.92	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.57	24.00	0.00	53.00	-0.51	-0.52	2.99	8.50	0.00	1.83	0.00	0.00
230.00	259.00	86.25	6.33	1.10	0.00	0.52	1.90	0.27	2.56	31.71	24.00	0.00	54.00	-0.51	-0.52	5.30	0.00	8.95	3.22	5.73	1.25
231.00	259.00	87.27	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.71	24.00	0.00	54.00	-0.51	-0.52	4.02	7.35	0.00	2.45	0.00	0.00
232.00	259.00	95.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.71	24.00	0.00	54.00	-0.51	-0.52	3.35	8.15	0.00	2.05	0.00	0.00
233.00	259.00	103.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.71	24.00	0.00	54.00	-0.51	-0.52	3.41	8.00	0.00	2.08	0.00	0.00
234.00	259.00	111.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.86	24.00	0.00	55.00	-0.51	-0.52	3.42	8.00	0.00	2.09	0.00	0.00
235.00	259.00	118.98	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.86	24.00	0.00	55.00	-0.51	-0.52	3.85	7.57	0.00	2.35	0.00	0.00
236.00	259.00	127.25	0.00	1.10	47.00	0.52	1.90	0.27	2.56	31.86	24.00	0.00	55.00	-0.51	-0.52	3.22	8.27	0.00	1.97	0.00	0.00
237.00	259.00	135.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	32.00	24.00	0.00	56.00	-0.51	-0.52	3.24	8.17	0.00	1.98	0.00	0.00
238.00	259.00	143.42	0.00	1.10	47.00	0.52	1.90	0.27	2.56	32.00	24.00	0.00	56.00	-0.51	-0.52	3.40	8.00	0.00	2.08	0.00	0.00
239.00	259.00	151.18	0.00	1.10	47.00	0.52	1.90	0.27	2.56	32.00	24.00	0.00	56.00	-0.51	-0.52	3.64	7.77	0.00	2.23	0.00	0.00
240.00	259.00	158.13	6.95	1.10	0.00	0.52	1.90	0.27	2.56	32.14	24.00	0.00	57.00	-0.51	-0.52	4.58	0.00	5.46	2.79	2.67	0.35
241.00	613.00	0.00	0.00	0.79	71.00	0.25	3.28	0.08	9.22	25.43	24.00	0.00	10.00	0.30	0.35	0.00	0.00	0.00	0.00	0.00	0.00
242.00	613.00	8.00	0.00	0.79	71.00	0.25	3.28	0.08	9.22	25.57	24.00	0.00	11.00	0.30	0.35	12.08	8.00	0.00	16.64	0.00	0.00
243.00	613.00	17.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.57	24.00	0.00	11.00	0.30	0.35	18.07	9.00	0.00	24.50	0.00	0.00
244.00	613.00	25.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.57	24.00	0.00	11.00	0.30	0.35	22.43	8.00	0.00	30.24	0.00	0.00
245.00	613.00	33.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.71	24.00	0.00	12.00	0.30	0.35	24.80	8.00	0.00	33.26	0.00	0.00
246.00	613.00	37.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.71	24.00	0.00	12.00	0.30	0.35	35.37	4.00	0.00	48.04	0.00	0.00
247.00	613.00	45.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.71	24.00	0.00	12.00	0.30	0.35	31.84	8.00	0.00	42.63	0.00	0.00
248.00	613.00	53.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.86	24.00	0.00	13.00	0.30	0.35	29.92	8.00	0.00	39.79	0.00	0.00
249.00	613.00	61.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.86	24.00	0.00	13.00	0.30	0.35	28.88	8.00	0.00	38.29	0.00	0.00
250.00	613.00	69.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	25.86	24.00	0.00	13.00	0.30	0.35	28.31	8.00	0.00	37.50	0.00	0.00
251.00	613.00	77.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.00	24.00	0.00	14.00	0.30	0.35	28.00	8.00	0.00	37.08	0.00	0.00
252.00	613.00	85.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.00	24.00	0.00	14.00	0.30	0.35	27.83	8.00	0.00	36.86	0.00	0.00
253.00	613.00	93.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.00	24.00	0.00	14.00	0.30	0.35	27.74	8.00	0.00	36.75	0.00	0.00
254.00	613.00	101.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.14	24.00	0.00	15.00	0.30	0.35	27.69	8.00	0.00	36.69	0.00	0.00
255.00	613.00	109.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.14	24.00	0.00	15.00	0.30	0.35	27.66	8.00	0.00	36.66	0.00	0.00
256.00	613.00	117.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.14	24.00	0.00	15.00	0.30	0.35	27.65	8.00	0.00	36.64	0.00	0.00

257.00	613.00	125.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.29	24.00	0.00	16.00	0.30	0.35	27.64	8.00	0.00	36.63	0.00	0.00
258.00	613.00	133.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.29	24.00	0.00	16.00	0.30	0.35	27.64	8.00	0.00	36.63	0.00	0.00
259.00	613.00	141.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.29	24.00	0.00	16.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
260.00	613.00	149.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.43	24.00	0.00	17.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
261.00	613.00	157.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.43	24.00	0.00	17.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
262.00	613.00	165.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.43	24.00	0.00	17.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
263.00	613.00	173.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.57	24.00	0.00	18.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
264.00	613.00	185.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.57	24.00	0.00	18.00	0.30	0.35	20.38	12.00	0.00	26.57	0.00	0.00
265.00	613.00	193.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.57	24.00	0.00	18.00	0.30	0.35	23.69	8.00	0.00	31.33	0.00	0.00
266.00	613.00	201.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.71	24.00	0.00	19.00	0.30	0.35	25.49	8.00	0.00	33.84	0.00	0.00
267.00	613.00	209.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.71	24.00	0.00	19.00	0.30	0.35	26.46	8.00	0.00	35.16	0.00	0.00
268.00	613.00	217.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.71	24.00	0.00	19.00	0.30	0.35	27.00	8.00	0.00	35.85	0.00	0.00
269.00	613.00	225.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.86	24.00	0.00	20.00	0.30	0.35	27.29	8.00	0.00	36.22	0.00	0.00
270.00	613.00	235.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.86	24.00	0.00	20.00	0.30	0.35	23.57	10.00	0.00	31.01	0.00	0.00
271.00	613.00	243.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	26.86	24.00	0.00	20.00	0.30	0.35	25.42	8.00	0.00	33.67	0.00	0.00
272.00	613.00	251.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.00	24.00	0.00	21.00	0.30	0.35	26.43	8.00	0.00	35.07	0.00	0.00
273.00	613.00	259.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.00	24.00	0.00	21.00	0.30	0.35	26.98	8.00	0.00	35.80	0.00	0.00
274.00	613.00	275.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.14	24.00	0.00	22.00	0.30	0.35	14.84	16.00	0.00	19.05	0.00	0.00
275.00	613.00	283.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.14	24.00	0.00	22.00	0.30	0.35	20.67	8.00	0.00	27.37	0.00	0.00
276.00	613.00	291.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.14	24.00	0.00	22.00	0.30	0.35	23.85	8.00	0.00	31.75	0.00	0.00
277.00	613.00	299.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.29	24.00	0.00	23.00	0.30	0.35	25.57	8.00	0.00	34.06	0.00	0.00
278.00	613.00	307.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.29	24.00	0.00	23.00	0.30	0.35	26.51	8.00	0.00	35.27	0.00	0.00
279.00	613.00	315.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.29	24.00	0.00	23.00	0.30	0.35	27.02	8.00	0.00	35.91	0.00	0.00
280.00	613.00	323.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.43	24.00	0.00	24.00	0.30	0.35	27.30	8.00	0.00	36.25	0.00	0.00
281.00	613.00	331.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.43	24.00	0.00	24.00	0.30	0.35	27.45	8.00	0.00	36.43	0.00	0.00
282.00	613.00	339.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.43	24.00	0.00	24.00	0.30	0.35	27.53	8.00	0.00	36.52	0.00	0.00
283.00	613.00	347.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.57	24.00	0.00	25.00	0.30	0.35	27.58	8.00	0.00	36.57	0.00	0.00
284.00	613.00	355.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.57	24.00	0.00	25.00	0.30	0.35	27.60	8.00	0.00	36.59	0.00	0.00
285.00	613.00	363.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.57	24.00	0.00	25.00	0.30	0.35	27.62	8.00	0.00	36.61	0.00	0.00
286.00	613.00	371.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.71	24.00	0.00	26.00	0.30	0.35	27.62	8.00	0.00	36.61	0.00	0.00

287.00	613.00	379.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.71	24.00	0.00	26.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
288.00	613.00	387.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.71	24.00	0.00	26.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
289.00	613.00	395.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.86	24.00	0.00	27.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
290.00	613.00	403.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.86	24.00	0.00	27.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
291.00	613.00	411.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	27.86	24.00	0.00	27.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
292.00	613.00	417.17	6.17	0.76	0.00	0.24	3.13	0.08	9.11	28.00	24.00	0.00	28.00	0.30	0.35	31.76	0.00	28.20	42.41	-14.21	-0.33
293.00	613.00	419.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	28.00	24.00	0.00	28.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
294.00	613.00	425.00	6.00	0.76	0.00	0.24	3.13	0.08	9.11	28.00	24.00	0.00	28.00	0.30	0.35	32.17	0.00	49.85	42.99	6.86	0.17
295.00	613.00	427.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	28.00	24.00	0.00	28.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
296.00	613.00	435.00	0.00	0.76	71.00	0.24	3.13	0.08	9.11	28.00	24.00	0.00	28.00	0.30	0.35	27.63	8.00	0.00	36.62	0.00	0.00
297.00	613.00	440.75	5.75	0.76	0.00	0.24	3.13	0.08	9.11	28.14	24.00	0.00	29.00	0.30	0.35	32.79	0.00	48.00	43.87	4.14	0.11
298.00	625.00	0.00	0.00	0.81	71.60	0.32	2.60	0.12	5.71	28.71	26.00	1.00	17.00	0.08	0.10	0.00	0.00	0.00	0.00	0.00	0.00
299.00	625.00	8.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	28.86	26.00	1.00	18.00	0.08	0.10	12.21	8.00	0.00	13.24	0.00	0.00
300.00	625.00	16.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	28.86	26.00	1.00	18.00	0.08	0.10	17.42	8.00	0.00	18.78	0.00	0.00
301.00	625.00	24.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	28.86	26.00	1.00	18.00	0.08	0.10	19.64	8.00	0.00	21.11	0.00	0.00
302.00	625.00	32.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.00	26.00	1.00	19.00	0.08	0.10	20.58	8.00	0.00	22.08	0.00	0.00
303.00	625.00	40.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.00	26.00	1.00	19.00	0.08	0.10	20.99	8.00	0.00	22.49	0.00	0.00
304.00	625.00	48.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.00	26.00	1.00	19.00	0.08	0.10	21.16	8.00	0.00	22.66	0.00	0.00
305.00	625.00	56.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.14	26.00	1.00	20.00	0.08	0.10	21.23	8.00	0.00	22.73	0.00	0.00
306.00	625.00	64.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.14	26.00	1.00	20.00	0.08	0.10	21.27	8.00	0.00	22.76	0.00	0.00
307.00	625.00	72.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.14	26.00	1.00	20.00	0.08	0.10	21.28	8.00	0.00	22.78	0.00	0.00
308.00	625.00	80.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.29	26.00	1.00	21.00	0.08	0.10	21.28	8.00	0.00	22.78	0.00	0.00
309.00	625.00	88.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.29	26.00	1.00	21.00	0.08	0.10	21.29	8.00	0.00	22.78	0.00	0.00
310.00	625.00	96.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.29	26.00	1.00	21.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
311.00	625.00	104.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.43	26.00	1.00	22.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
312.00	625.00	108.25	4.25	0.80	0.00	0.27	2.57	0.11	6.50	29.43	26.00	1.00	22.00	0.08	0.10	31.74	0.00	24.30	34.25	-9.95	-0.35
313.00	625.00	112.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.43	26.00	1.00	22.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
314.00	625.00	120.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.43	26.00	1.00	22.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
315.00	625.00	128.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.57	26.00	1.00	23.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
316.00	625.00	136.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.57	26.00	1.00	23.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00

317.00	625.00	144.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.57	26.00	1.00	23.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
318.00	625.00	152.00	0.00	0.80	71.60	0.27	2.57	0.11	6.50	29.71	26.00	1.00	24.00	0.08	0.10	21.29	8.00	0.00	22.79	0.00	0.00
319.00	625.00	156.42	4.42	0.80	0.00	0.27	2.57	0.11	6.50	29.71	26.00	1.00	24.00	0.08	0.10	31.17	0.00	53.40	33.63	19.77	0.54
322.00	663.00	0.00	0.00	1.14	74.00	0.13	1.28	0.11	6.60	34.57	23.00	0.00	77.00	-0.90	-0.96	0.00	0.00	0.00	0.00	0.00	0.00
323.00	663.00	8.00	0.00	1.14	74.00	0.13	1.28	0.11	6.60	34.57	23.00	0.00	77.00	-0.90	-0.96	25.69	8.00	0.00	10.29	0.00	0.00
324.00	663.00	14.42	6.42	1.14	0.00	0.13	1.28	0.11	6.60	34.71	23.00	0.00	78.00	-0.90	-0.96	43.41	0.00	47.30	17.47	29.83	0.71
325.00	663.00	16.00	0.00	1.16	74.00	0.11	1.29	0.08	8.27	34.71	23.00	0.00	78.00	-0.90	-0.96	37.63	8.00	0.00	15.25	0.00	0.00
326.00	663.00	24.00	0.00	1.16	74.00	0.11	1.29	0.08	8.27	34.71	23.00	0.00	78.00	-0.90	-0.96	49.21	8.00	0.00	19.98	0.00	0.00
328.00	663.00	29.83	5.83	1.15	0.00	0.18	1.29	0.14	4.96	34.71	23.00	0.00	78.00	-0.90	-0.96	48.15	0.00	52.00	19.78	32.22	0.76
329.00	663.00	32.00	0.00	1.15	74.00	0.18	1.29	0.14	4.96	34.71	23.00	0.00	78.00	-0.90	-0.96	35.55	8.00	0.00	14.85	0.00	0.00
330.00	663.00	40.00	8.00	1.15	0.00	0.18	1.29	0.14	4.96	34.86	23.00	0.00	79.00	-0.90	-0.96	31.07	0.00	0.15	13.06	-12.91	-1.99
331.00	663.00	40.00	0.00	1.15	74.00	0.18	1.29	0.14	4.96	34.86	23.00	0.00	79.00	-0.90	-0.96	31.07	8.00	0.00	13.06	0.00	0.00
332.00	663.00	48.00	0.00	1.15	74.00	0.18	1.29	0.14	4.96	34.86	23.00	0.00	79.00	-0.90	-0.96	29.61	8.00	0.00	12.43	0.00	0.00
333.00	663.00	54.25	6.25	1.15	0.00	0.18	1.29	0.14	4.96	34.86	23.00	0.00	79.00	-0.90	-0.96	37.20	0.00	32.75	15.40	17.35	0.20
334.00	663.00	56.00	0.00	1.15	74.00	0.18	1.29	0.14	4.96	34.86	23.00	0.00	79.00	-0.90	-0.96	29.13	8.00	0.00	12.22	0.00	0.00
335.00	663.00	62.50	6.50	1.15	0.00	0.18	1.29	0.14	4.96	35.00	23.00	0.00	80.00	-0.90	-0.96	35.73	0.00	85.60	14.81	70.79	3.97
336.00	664.00	0.00	0.00	0.66	79.00	0.04	0.52	0.09	8.10	27.43	26.00	1.00	4.00	-1.04	-1.31	0.00	0.00	0.00	0.00	0.00	0.00
337.00	664.00	8.00	0.00	0.66	79.00	0.04	0.52	0.08	8.67	27.57	26.00	1.00	5.00	-1.04	-1.31	82.47	8.00	0.00	25.76	0.00	0.00
338.00	664.00	16.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.57	26.00	1.00	5.00	-1.04	-1.31	122.06	8.00	0.00	40.23	0.00	0.00
339.00	664.00	24.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.57	26.00	1.00	5.00	-1.04	-1.31	144.67	8.00	0.00	49.75	0.00	0.00
340.00	664.00	32.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.71	26.00	1.00	6.00	-1.04	-1.31	156.66	8.00	0.00	55.62	0.00	0.00
341.00	664.00	40.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.71	26.00	1.00	6.00	-1.04	-1.31	163.02	8.00	0.00	59.25	0.00	0.00
342.00	664.00	48.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.71	26.00	1.00	6.00	-1.04	-1.31	166.40	8.00	0.00	61.48	0.00	0.00
343.00	664.00	56.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.86	26.00	1.00	7.00	-1.04	-1.31	168.19	8.00	0.00	62.86	0.00	0.00
344.00	664.00	64.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.86	26.00	1.00	7.00	-1.04	-1.31	169.14	8.00	0.00	63.72	0.00	0.00
345.00	664.00	72.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	27.86	26.00	1.00	7.00	-1.04	-1.31	169.64	8.00	0.00	64.24	0.00	0.00
346.00	664.00	79.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.00	26.00	1.00	8.00	-1.04	-1.31	183.92	7.00	0.00	68.58	0.00	0.00
347.00	664.00	87.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.00	26.00	1.00	8.00	-1.04	-1.31	177.49	8.00	0.00	67.24	0.00	0.00
348.00	664.00	95.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.00	26.00	1.00	8.00	-1.04	-1.31	174.07	8.00	0.00	66.42	0.00	0.00
349.00	664.00	103.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.14	26.00	1.00	9.00	-1.04	-1.31	172.26	8.00	0.00	65.91	0.00	0.00



350.00	664.00	107.00	4.00	0.68	0.00	0.04	0.54	0.08	8.75	28.14	26.00	1.00	9.00	-1.04	-1.31	235.18	0.00	126.00	83.50	42.50	-0.81
351.00	664.00	111.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.14	26.00	1.00	9.00	-1.04	-1.31	171.30	8.00	0.00	65.59	0.00	0.00
352.00	664.00	119.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.14	26.00	1.00	9.00	-1.04	-1.31	170.79	8.00	0.00	65.40	0.00	0.00
353.00	664.00	127.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.29	26.00	1.00	10.00	-1.04	-1.31	170.52	8.00	0.00	65.28	0.00	0.00
354.00	664.00	130.08	3.08	0.68	0.00	0.04	0.54	0.08	8.75	28.29	26.00	1.00	10.00	-1.04	-1.31	251.60	0.00	367.00	87.75	279.25	1.86
355.00	664.00	135.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.29	26.00	1.00	10.00	-1.04	-1.31	170.38	8.00	0.00	65.21	0.00	0.00
356.00	664.00	143.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.29	26.00	1.00	10.00	-1.04	-1.31	170.30	8.00	0.00	65.16	0.00	0.00
357.00	664.00	151.00	0.00	0.68	79.00	0.04	0.54	0.08	8.75	28.43	26.00	1.00	11.00	-1.04	-1.31	170.26	8.00	0.00	65.13	0.00	0.00
358.00	664.00	153.80	2.80	0.68	0.00	0.04	0.54	0.08	8.75	28.43	26.00	1.00	11.00	-1.04	-1.31	257.03	0.00	502.00	89.12	412.88	3.30
386.00	668.00	0.00	0.00	0.72	63.00	0.03	0.27	0.11	6.10	28.43	27.00	1.00	4.00	-1.90	-2.04	0.00	0.00	0.00	0.00	0.00	0.00
387.00	668.00	8.00	0.00	0.72	63.00	0.03	0.27	0.11	6.10	28.57	27.00	1.00	5.00	-1.90	-2.04	96.10	8.00	0.00	13.99	0.00	0.00
388.00	668.00	16.00	0.00	0.72	63.00	0.03	0.27	0.13	5.42	28.57	27.00	1.00	5.00	-1.90	-2.04	120.67	8.00	0.00	18.43	0.00	0.00
389.00	668.00	24.00	0.00	0.81	63.00	0.04	0.31	0.14	4.90	28.57	27.00	1.00	5.00	-1.90	-2.04	102.66	8.00	0.00	16.26	0.00	0.00
390.00	668.00	32.00	8.00	0.72	0.00	0.04	0.27	0.15	4.75	28.71	27.00	1.00	6.00	-1.90	-2.04	110.90	0.00	68.00	17.86	50.14	-0.88
391.00	668.00	32.00	8.00	0.72	0.00	0.04	0.27	0.15	4.75	28.71	27.00	1.00	6.00	-1.90	-2.04	110.90	0.00	249.00	17.86	231.14	9.65
392.00	668.00	32.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	28.71	27.00	1.00	6.00	-1.90	-2.04	110.90	8.00	0.00	17.86	0.00	0.00
393.00	668.00	40.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	28.71	27.00	1.00	6.00	-1.90	-2.04	109.23	8.00	0.00	17.66	0.00	0.00
394.00	668.00	45.25	5.25	0.72	0.00	0.04	0.27	0.15	4.75	28.71	27.00	1.00	6.00	-1.90	-2.04	162.42	0.00	224.00	24.99	199.01	4.70
395.00	668.00	48.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	28.71	27.00	1.00	6.00	-1.90	-2.04	108.71	8.00	0.00	17.59	0.00	0.00
396.00	668.00	56.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	28.86	27.00	1.00	7.00	-1.90	-2.04	108.55	8.00	0.00	17.56	0.00	0.00
398.00	668.00	64.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	28.86	27.00	1.00	7.00	-1.90	-2.04	108.50	8.00	0.00	17.55	0.00	0.00
399.00	668.00	72.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	28.86	27.00	1.00	7.00	-1.90	-2.04	108.48	8.00	0.00	17.55	0.00	0.00
400.00	668.00	80.00	0.00	0.72	63.00	0.04	0.27	0.15	4.75	29.00	27.00	1.00	8.00	-1.90	-2.04	108.48	8.00	0.00	17.55	0.00	0.00
402.00	669.00	0.00	0.00	1.16	110.00	0.95	4.97	0.19	3.62	32.00	27.00	1.00	35.00	0.36	0.39	0.00	0.00	0.00	0.00	0.00	0.00
403.00	669.00	8.00	0.00	1.18	110.00	0.97	5.07	0.19	3.64	32.00	27.00	1.00	35.00	0.36	0.39	4.95	8.00	0.00	6.95	0.00	0.00
404.00	669.00	16.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.00	27.00	1.00	35.00	0.36	0.39	8.16	8.00	0.00	11.47	0.00	0.00
405.00	669.00	24.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.14	27.00	1.00	36.00	0.36	0.39	9.09	8.00	0.00	12.72	0.00	0.00
406.00	669.00	32.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.14	27.00	1.00	36.00	0.36	0.39	9.37	8.00	0.00	13.08	0.00	0.00
407.00	669.00	40.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.14	27.00	1.00	36.00	0.36	0.39	9.45	8.00	0.00	13.18	0.00	0.00
408.00	669.00	48.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.29	27.00	1.00	37.00	0.36	0.39	9.47	8.00	0.00	13.21	0.00	0.00

409.00	669.00	56.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.29	27.00	1.00	37.00	0.36	0.39	9.48	8.00	0.00	13.21	0.00	0.00
410.00	669.00	64.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.29	27.00	1.00	37.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
411.00	669.00	72.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.43	27.00	1.00	38.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
412.00	669.00	80.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.43	27.00	1.00	38.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
413.00	669.00	88.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.43	27.00	1.00	38.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
414.00	669.00	96.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.57	27.00	1.00	39.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
415.00	669.00	104.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.57	27.00	1.00	39.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
416.00	669.00	112.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.57	27.00	1.00	39.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
417.00	669.00	118.75	6.75	1.17	0.00	0.77	5.03	0.15	4.53	32.71	27.00	1.00	40.00	0.36	0.39	11.48	0.00	13.30	16.11	-2.81	-0.15
418.00	669.00	120.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.71	27.00	1.00	40.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
419.00	669.00	128.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.71	27.00	1.00	40.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
420.00	669.00	136.00	0.00	1.17	110.00	0.77	5.03	0.15	4.53	32.71	27.00	1.00	40.00	0.36	0.39	9.48	8.00	0.00	13.22	0.00	0.00
421.00	669.00	142.00	6.00	1.17	0.00	0.77	5.03	0.15	4.53	32.86	27.00	1.00	41.00	0.36	0.39	12.88	0.00	18.60	18.14	0.46	0.05
448.00	690.00	0.00	0.00	1.40	140.00	1.47	3.38	0.43	1.60	36.86	31.00	2.00	39.00	-0.05	-0.19	0.00	0.00	0.00	0.00	0.00	0.00
449.00	690.00	9.00	0.00	1.40	140.00	1.47	3.39	0.43	1.60	37.00	31.00	2.00	40.00	-0.05	-0.19	0.94	9.00	0.00	1.26	0.00	0.00
450.00	690.00	16.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.00	31.00	2.00	40.00	-0.05	-0.19	2.27	7.00	0.00	2.77	0.00	0.00
451.00	690.00	24.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.00	31.00	2.00	40.00	-0.05	-0.19	1.52	8.00	0.00	1.97	0.00	0.00
452.00	690.00	32.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.14	31.00	2.00	41.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
453.00	690.00	40.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.14	31.00	2.00	41.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
454.00	690.00	48.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.14	31.00	2.00	41.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
455.00	690.00	56.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.29	31.00	2.00	42.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
456.00	690.00	64.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.29	31.00	2.00	42.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
457.00	690.00	73.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.29	31.00	2.00	42.00	-0.05	-0.19	0.97	9.00	0.00	1.32	0.00	0.00
458.00	690.00	80.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.43	31.00	2.00	43.00	-0.05	-0.19	2.27	7.00	0.00	2.77	0.00	0.00
459.00	690.00	84.00	4.00	1.40	0.00	1.46	3.38	0.43	1.60	37.43	31.00	2.00	43.00	-0.05	-0.19	8.57	0.00	4.92	8.95	-4.03	-0.50
460.00	690.00	88.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.43	31.00	2.00	43.00	-0.05	-0.19	1.52	8.00	0.00	1.97	0.00	0.00
461.00	690.00	96.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.43	31.00	2.00	43.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
462.00	690.00	104.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.57	31.00	2.00	44.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
463.00	690.00	108.00	4.00	1.40	0.00	1.46	3.38	0.43	1.60	37.57	31.00	2.00	44.00	-0.05	-0.19	8.44	0.00	17.00	8.76	8.24	0.95
464.00	690.00	111.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.57	31.00	2.00	44.00	-0.05	-0.19	2.30	7.00	0.00	2.82	0.00	0.00

465.00	690.00	119.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.57	31.00	2.00	44.00	-0.05	-0.19	1.52	8.00	0.00	1.97	0.00	0.00
466.00	690.00	127.00	0.00	1.40	140.00	1.46	3.38	0.43	1.60	37.71	31.00	2.00	45.00	-0.05	-0.19	1.49	8.00	0.00	1.93	0.00	0.00
467.00	690.00	132.00	5.00	1.40	0.00	1.46	3.38	0.43	1.60	37.71	31.00	2.00	45.00	-0.05	-0.19	5.47	0.00	3.64	6.00	-2.36	-0.44
468.00	696.00	0.00	0.00	0.76	47.00	0.31	2.15	0.15	4.76	28.71	24.00	0.00	33.00	0.11	-0.03	0.00	0.00	0.00	0.00	0.00	0.00
469.00	696.00	8.00	0.00	0.75	47.00	0.31	2.10	0.15	4.74	28.86	24.00	0.00	34.00	0.11	-0.03	7.19	8.00	0.00	8.12	0.00	0.00
470.00	696.00	16.00	0.00	0.76	47.00	0.31	2.14	0.15	4.76	28.86	24.00	0.00	34.00	0.11	-0.03	9.31	8.00	0.00	10.94	0.00	0.00
471.00	696.00	24.00	0.00	0.71	47.00	0.30	2.01	0.15	4.68	28.86	24.00	0.00	34.00	0.11	-0.03	10.44	8.00	0.00	12.57	0.00	0.00
472.00	696.00	32.00	0.00	0.75	47.00	0.43	2.12	0.20	3.39	29.00	24.00	0.00	35.00	0.11	-0.03	6.48	8.00	0.00	8.37	0.00	0.00
473.00	696.00	40.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.00	24.00	0.00	35.00	0.11	-0.03	5.85	8.00	0.00	7.56	0.00	0.00
474.00	696.00	48.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.00	24.00	0.00	35.00	0.11	-0.03	5.72	8.00	0.00	7.34	0.00	0.00
475.00	696.00	56.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.14	24.00	0.00	36.00	0.11	-0.03	5.69	8.00	0.00	7.29	0.00	0.00
476.00	696.00	60.00	4.00	0.74	0.00	0.43	2.09	0.21	3.38	29.14	24.00	0.00	36.00	0.11	-0.03	12.92	0.00	3.34	14.78	-11.44	-0.59
477.00	696.00	64.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.14	24.00	0.00	36.00	0.11	-0.03	5.69	8.00	0.00	7.27	0.00	0.00
478.00	696.00	72.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.14	24.00	0.00	36.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
479.00	696.00	80.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.29	24.00	0.00	37.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
480.00	696.00	88.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.29	24.00	0.00	37.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
481.00	696.00	96.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.29	24.00	0.00	37.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
482.00	696.00	104.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.43	24.00	0.00	38.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
483.00	696.00	109.00	5.00	0.74	0.00	0.43	2.09	0.21	3.38	29.43	24.00	0.00	38.00	0.11	-0.03	10.52	0.00	1.98	12.37	-10.39	-0.65
484.00	696.00	112.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.43	24.00	0.00	38.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
485.00	696.00	120.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.43	24.00	0.00	38.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
486.00	696.00	128.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.57	24.00	0.00	39.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
487.00	696.00	136.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.57	24.00	0.00	39.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
488.00	696.00	144.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.57	24.00	0.00	39.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
489.00	696.00	152.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.71	24.00	0.00	40.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
490.00	696.00	155.25	3.25	0.74	0.00	0.43	2.09	0.21	3.38	29.71	24.00	0.00	40.00	0.11	-0.03	15.06	0.00	38.50	16.87	21.63	1.47
491.00	696.00	160.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.71	24.00	0.00	40.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
492.00	696.00	168.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.71	24.00	0.00	40.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
493.00	696.00	176.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.86	24.00	0.00	41.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
494.00	696.00	180.25	4.25	0.74	0.00	0.43	2.09	0.21	3.38	29.86	24.00	0.00	41.00	0.11	-0.03	12.27	0.00	2.58	14.13	-11.55	-0.63

495.00	696.00	184.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.86	24.00	0.00	41.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
496.00	696.00	192.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	29.86	24.00	0.00	41.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
497.00	696.00	200.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.00	24.00	0.00	42.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
498.00	696.00	208.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.00	24.00	0.00	42.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
499.00	696.00	216.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.00	24.00	0.00	42.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
500.00	696.00	224.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.14	24.00	0.00	43.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
501.00	696.00	226.50	2.50	0.74	0.00	0.43	2.09	0.21	3.38	30.14	24.00	0.00	43.00	0.11	-0.03	17.57	0.00	6.11	19.27	-13.16	-0.49
502.00	696.00	232.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.14	24.00	0.00	43.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
503.00	696.00	240.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.14	24.00	0.00	43.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
504.00	696.00	248.00	0.00	0.74	47.00	0.43	2.09	0.21	3.38	30.29	24.00	0.00	44.00	0.11	-0.03	5.68	8.00	0.00	7.27	0.00	0.00
505.00	696.00	252.33	4.33	0.74	0.00	0.43	2.09	0.21	3.38	30.29	24.00	0.00	44.00	0.11	-0.03	12.07	0.00	9.48	13.93	-4.45	-0.12
506.00	715.00	0.00	0.00	1.12	110.00	0.37	5.73	0.07	10.61	28.29	28.00	1.00	1.00	0.44	0.56	0.00	0.00	0.00	0.00	0.00	0.00
507.00	715.00	12.50	0.00	1.12	110.00	0.37	5.73	0.07	10.61	28.29	28.00	1.00	1.00	0.44	0.56	8.62	12.50	0.00	13.62	0.00	0.00
508.00	715.00	19.25	6.75	1.12	0.00	0.37	5.73	0.07	10.61	28.43	28.00	1.00	1.00	0.44	0.56	18.09	0.00	22.20	29.11	-6.91	-0.17
509.00	727.00	0.00	0.00	1.48	150.00	0.88	10.72	0.08	8.45	30.43	29.00	1.00	10.00	0.70	0.91	0.00	0.00	0.00	0.00	0.00	0.00
510.00	727.00	12.00	0.00	1.42	150.00	0.85	10.28	0.08	8.36	30.57	29.00	1.00	11.00	0.70	0.91	5.51	12.00	0.00	10.97	0.00	0.00
511.00	727.00	16.58	4.58	1.46	0.00	0.86	10.57	0.08	8.53	30.57	29.00	1.00	11.00	0.70	0.91	13.68	0.00	11.60	29.66	-18.06	-0.41
512.00	727.00	24.00	0.00	1.46	150.00	0.86	10.57	0.08	8.53	30.57	29.00	1.00	11.00	0.70	0.91	7.49	12.00	0.00	14.15	0.00	0.00
513.00	727.00	36.00	0.00	1.46	150.00	0.86	10.57	0.08	8.53	30.71	29.00	1.00	12.00	0.70	0.91	8.29	12.00	0.00	15.20	0.00	0.00
514.00	727.00	37.42	1.42	1.46	0.00	0.86	10.57	0.08	8.53	30.71	29.00	1.00	12.00	0.70	0.91	20.30	0.00	30.90	44.59	-13.69	-0.13
515.00	728.00	0.00	0.00	0.96	88.00	0.63	3.98	0.16	4.38	29.43	27.00	1.00	14.00	0.45	0.35	0.00	0.00	0.00	0.00	0.00	0.00
516.00	728.00	11.00	0.00	0.96	88.00	0.63	3.98	0.16	4.38	29.43	27.00	1.00	14.00	0.45	0.35	4.04	11.00	0.00	6.75	0.00	0.00
517.00	728.00	23.00	0.00	0.92	88.00	0.61	3.82	0.16	4.34	29.57	27.00	1.00	15.00	0.45	0.35	4.15	12.00	0.00	7.23	0.00	0.00
518.00	728.00	35.50	0.00	0.92	88.00	0.61	3.82	0.16	4.34	29.57	27.00	1.00	15.00	0.45	0.35	3.82	12.50	0.00	6.76	0.00	0.00
519.00	728.00	43.55	8.05	0.94	0.00	0.69	3.90	0.18	3.91	29.71	27.00	1.00	16.00	0.45	0.35	6.56	0.00	0.12	11.00	-10.88	-0.82
520.00	728.00	47.17	0.00	0.94	88.00	0.69	3.90	0.18	3.91	29.71	27.00	1.00	16.00	0.45	0.35	3.45	11.67	0.00	6.15	0.00	0.00
521.00	728.00	48.33	1.16	0.94	0.00	0.69	3.90	0.18	3.91	29.71	27.00	1.00	16.00	0.45	0.35	22.31	0.00	13.40	33.27	-19.87	-0.42
522.00	728.00	60.00	0.00	0.94	88.00	0.69	3.90	0.18	3.91	29.71	27.00	1.00	16.00	0.45	0.35	2.82	12.83	0.00	5.10	0.00	0.00
523.00	728.00	71.00	0.00	0.94	88.00	0.69	3.90	0.18	3.91	29.86	27.00	1.00	17.00	0.45	0.35	3.76	11.00	0.00	6.59	0.00	0.00
524.00	728.00	73.67	2.67	0.94	0.00	0.69	3.90	0.18	3.91	29.86	27.00	1.00	17.00	0.45	0.35	17.04	0.00	35.40	26.09	9.31	0.50

525.00	728.00	75.25	4.25	0.94	0.00	0.69	3.90	0.18	3.91	29.86	27.00	1.00	17.00	0.45	0.35	12.88	0.00	12.60	20.24	-7.64	-0.20
526.00	728.00	83.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	29.86	27.00	1.00	17.00	0.45	0.35	2.98	12.50	0.00	5.38	0.00	0.00
527.00	728.00	95.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.00	27.00	1.00	18.00	0.45	0.35	3.17	12.00	0.00	5.65	0.00	0.00
528.00	728.00	108.00	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.00	27.00	1.00	18.00	0.45	0.35	2.92	12.50	0.00	5.25	0.00	0.00
529.00	728.00	119.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.14	27.00	1.00	19.00	0.45	0.35	3.45	11.50	0.00	6.11	0.00	0.00
530.00	728.00	131.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.14	27.00	1.00	19.00	0.45	0.35	3.22	12.00	0.00	5.76	0.00	0.00
531.00	728.00	143.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.29	27.00	1.00	20.00	0.45	0.35	3.20	12.00	0.00	5.71	0.00	0.00
532.00	728.00	155.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.29	27.00	1.00	20.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
533.00	728.00	167.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.43	27.00	1.00	21.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
534.00	728.00	179.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.43	27.00	1.00	21.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
535.00	728.00	191.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.57	27.00	1.00	22.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
536.00	728.00	203.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.57	27.00	1.00	22.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
537.00	728.00	215.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.71	27.00	1.00	23.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
538.00	728.00	227.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.71	27.00	1.00	23.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
539.00	728.00	239.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.86	27.00	1.00	24.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
540.00	728.00	251.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	30.86	27.00	1.00	24.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
541.00	728.00	263.50	0.00	0.94	88.00	0.69	3.90	0.18	3.91	31.00	27.00	1.00	25.00	0.45	0.35	3.19	12.00	0.00	5.70	0.00	0.00
542.00	728.00	273.50	10.00	0.94	0.00	0.69	3.90	0.18	3.91	31.00	27.00	1.00	25.00	0.45	0.35	4.55	0.00	5.73	7.86	-2.13	-0.05
543.00	734.00	0.00	0.00	0.56	60.00	0.13	1.69	0.08	8.93	28.57	27.00	1.00	7.00	0.20	0.04	0.00	0.00	0.00	0.00	0.00	0.00
544.00	734.00	13.50	0.00	0.57	60.00	0.23	1.73	0.13	5.25	28.71	27.00	1.00	8.00	0.20	0.04	6.02	13.50	0.00	8.12	0.00	0.00
545.00	734.00	15.92	2.42	0.57	0.00	0.23	1.73	0.13	5.25	28.71	27.00	1.00	8.00	0.20	0.04	30.38	0.00	48.40	34.49	13.91	0.32
546.00	734.00	24.50	0.00	0.57	60.00	0.23	1.73	0.13	5.25	28.71	27.00	1.00	8.00	0.20	0.04	9.78	11.00	0.00	13.12	0.00	0.00
547.00	734.00	34.83	10.33	0.57	0.00	0.23	1.73	0.13	5.25	28.86	27.00	1.00	9.00	0.20	0.04	11.64	0.00	9.80	15.71	-5.90	-0.41
548.00	735.00	0.00	0.00	1.28	120.00	1.19	11.49	0.10	6.71	29.86	24.00	0.00	38.00	0.90	1.13	0.00	0.00	0.00	0.00	0.00	0.00
549.00	735.00	8.00	0.00	1.28	120.00	1.19	11.49	0.10	6.71	29.86	24.00	0.00	38.00	0.90	1.13	4.69	8.00	0.00	11.86	0.00	0.00
550.00	735.00	16.50	0.00	1.28	120.00	1.19	11.49	0.10	6.71	30.00	24.00	0.00	39.00	0.90	1.13	6.40	8.50	0.00	15.09	0.00	0.00
551.00	735.00	20.55	4.05	1.28	0.00	1.19	11.49	0.10	6.71	30.00	24.00	0.00	39.00	0.90	1.13	11.27	0.00	11.80	28.68	-16.88	-0.41
552.00	735.00	26.00	9.50	1.28	0.00	1.19	11.49	0.10	6.71	30.00	24.00	0.00	39.00	0.90	1.13	6.42	0.00	8.64	14.21	-5.57	-0.20
553.00	736.00	0.00	0.00	1.46	161.00	0.38	3.69	0.10	6.69	31.00	30.00	2.00	3.00	0.02	-0.14	0.00	0.00	0.00	0.00	0.00	0.00
554.00	736.00	2.02	2.02	1.46	0.00	0.38	3.69	0.10	6.69	31.14	30.00	2.00	4.00	0.02	-0.14	36.29	0.00	44.80	32.32	12.48	0.21

555.00	736.00	8.00	8.00	1.46	0.00	0.38	3.69	0.10	6.69	31.14	30.00	2.00	4.00	0.02	-0.14	19.54	0.00	38.70	19.10	19.60	0.85
556.00	736.00	20.00	0.00	1.46	161.00	0.38	3.69	0.10	6.77	31.14	30.00	2.00	4.00	0.02	-0.14	5.72	20.00	0.00	6.73	0.00	0.00
557.00	736.00	31.50	11.50	1.46	0.00	0.38	3.69	0.10	6.77	31.29	30.00	2.00	5.00	0.02	-0.14	15.55	0.00	16.40	16.68	-0.28	-0.13
558.00	736.00	32.00	0.00	1.46	161.00	0.38	3.69	0.10	6.77	31.29	30.00	2.00	5.00	0.02	-0.14	14.78	12.00	0.00	15.97	0.00	0.00
559.00	736.00	42.00	10.00	1.46	0.00	0.38	3.69	0.10	6.77	31.29	30.00	2.00	5.00	0.02	-0.14	21.39	0.00	12.80	22.87	-10.07	-0.55
560.00	740.00	0.00	0.00	1.06	100.00	0.29	1.58	0.19	3.74	33.29	24.00	0.00	62.00	-0.52	-0.67	0.00	0.00	0.00	0.00	0.00	0.00
561.00	740.00	8.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.29	24.00	0.00	62.00	-0.52	-0.67	15.14	8.00	0.00	9.52	0.00	0.00
562.00	740.00	16.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.43	24.00	0.00	63.00	-0.52	-0.67	18.57	8.00	0.00	12.18	0.00	0.00
563.00	740.00	24.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.43	24.00	0.00	63.00	-0.52	-0.67	19.34	8.00	0.00	12.92	0.00	0.00
564.00	740.00	28.00	4.00	1.05	0.00	0.29	1.56	0.19	3.73	33.43	24.00	0.00	63.00	-0.52	-0.67	41.04	0.00	21.60	24.83	-3.23	-0.70
565.00	740.00	32.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.43	24.00	0.00	63.00	-0.52	-0.67	19.51	8.00	0.00	13.13	0.00	0.00
566.00	740.00	40.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.57	24.00	0.00	64.00	-0.52	-0.67	19.55	8.00	0.00	13.19	0.00	0.00
567.00	740.00	48.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.57	24.00	0.00	64.00	-0.52	-0.67	19.56	8.00	0.00	13.20	0.00	0.00
568.00	740.00	56.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.57	24.00	0.00	64.00	-0.52	-0.67	19.56	8.00	0.00	13.21	0.00	0.00
569.00	740.00	64.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.71	24.00	0.00	65.00	-0.52	-0.67	19.57	8.00	0.00	13.21	0.00	0.00
570.00	740.00	72.50	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.71	24.00	0.00	65.00	-0.52	-0.67	17.83	8.50	0.00	12.20	0.00	0.00
571.00	740.00	75.63	3.13	1.05	0.00	0.29	1.56	0.19	3.73	33.71	24.00	0.00	65.00	-0.52	-0.67	47.40	0.00	102.00	28.08	73.92	2.06
572.00	740.00	76.85	4.35	1.05	0.00	0.29	1.56	0.19	3.73	33.71	24.00	0.00	65.00	-0.52	-0.67	37.79	0.00	45.00	23.12	21.88	0.38
573.00	740.00	79.50	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.71	24.00	0.00	65.00	-0.52	-0.67	23.09	7.00	0.00	15.16	0.00	0.00
574.00	740.00	88.00	0.00	1.05	100.00	0.29	1.56	0.19	3.73	33.86	24.00	0.00	66.00	-0.52	-0.67	18.56	8.50	0.00	12.70	0.00	0.00
575.00	740.00	90.17	2.17	1.05	0.00	0.29	1.56	0.19	3.73	33.86	24.00	0.00	66.00	-0.52	-0.67	57.15	0.00	58.90	33.08	25.82	0.23
576.00	741.00	0.00	0.00	0.60	72.00	0.05	0.30	0.18	3.84	24.00	23.00	0.00	2.00	-1.24	-1.75	0.00	0.00	0.00	0.00	0.00	0.00
577.00	741.00	12.00	0.00	0.66	72.00	0.06	0.34	0.18	3.94	24.00	23.00	0.00	2.00	-1.24	-1.75	27.15	12.00	0.00	10.77	0.00	0.00
578.00	741.00	14.00	2.00	0.52	0.00	0.05	0.26	0.17	4.05	24.00	23.00	0.00	2.00	-1.24	-1.75	226.63	0.00	432.00	50.83	381.17	5.06
579.00	741.00	19.00	7.00	0.55	0.00	0.05	0.28	0.17	3.98	24.00	23.00	0.00	2.00	-1.24	-1.75	89.72	0.00	87.70	28.44	59.27	-0.09
580.00	741.00	24.50	0.00	0.55	72.00	0.05	0.28	0.17	3.98	24.14	23.00	0.00	3.00	-1.24	-1.75	34.44	12.50	0.00	15.97	0.00	0.00
581.00	741.00	36.00	0.00	0.55	72.00	0.05	0.28	0.17	3.98	24.14	23.00	0.00	3.00	-1.24	-1.75	41.01	11.50	0.00	18.58	0.00	0.00
582.00	741.00	46.75	10.75	0.55	0.00	0.05	0.28	0.17	3.98	24.29	23.00	0.00	4.00	-1.24	-1.75	47.74	0.00	71.60	20.95	50.65	0.56
583.00	741.00	48.00	0.00	0.55	72.00	0.05	0.28	0.17	3.98	24.29	23.00	0.00	4.00	-1.24	-1.75	38.40	12.00	0.00	18.37	0.00	0.00
584.00	741.00	60.00	0.00	0.55	72.00	0.05	0.28	0.17	3.98	24.29	23.00	0.00	4.00	-1.24	-1.75	38.08	12.00	0.00	18.31	0.00	0.00

585.00	741.00	70.25	10.25	0.55	0.00	0.05	0.28	0.17	3.98	24.43	23.00	0.00	5.00	-1.24	-1.75	51.59	0.00	66.30	21.99	44.32	0.14
586.00	743.00	0.00	0.00	1.78	175.00	0.34	3.08	0.11	6.27	33.00	31.00	2.00	8.00	-0.45	-0.52	0.00	0.00	0.00	0.00	0.00	0.00
587.00	743.00	13.00	0.00	1.78	180.00	0.34	3.08	0.11	6.27	33.00	31.00	2.00	8.00	-0.45	-0.52	13.89	13.00	0.00	9.06	0.00	0.00
588.00	743.00	22.83	9.83	1.78	0.00	0.34	3.08	0.11	6.27	33.14	31.00	2.00	9.00	-0.45	-0.52	24.96	0.00	38.80	16.22	22.58	1.06
589.00	819.00	0.00	0.00	1.27	100.00	0.12	2.00	0.06	11.94	28.86	23.00	0.00	35.00	-0.57	-0.61	0.00	0.00	0.00	0.00	0.00	0.00
590.00	819.00	8.35	0.00	1.48	100.00	0.11	2.33	0.05	14.18	28.86	23.00	0.00	35.00	-0.57	-0.61	28.85	8.35	0.00	15.91	0.00	0.00
591.00	819.00	15.80	0.00	1.48	100.00	0.13	2.33	0.06	12.41	29.00	23.00	0.00	36.00	-0.57	-0.61	47.71	7.45	0.00	26.51	0.00	0.00
592.00	819.00	28.82	0.00	1.16	50.00	0.17	1.83	0.09	7.51	29.00	23.00	0.00	36.00	-0.57	-0.61	35.12	13.02	0.00	20.36	0.00	0.00
593.00	819.00	36.10	0.00	1.17	50.00	0.17	1.84	0.09	7.52	29.00	23.00	0.00	36.00	-0.57	-0.61	31.99	7.28	0.00	18.56	0.00	0.00
595.00	819.00	45.00	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.14	23.00	0.00	37.00	-0.57	-0.61	25.78	8.90	0.00	15.04	0.00	0.00
596.00	819.00	52.43	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.14	23.00	0.00	37.00	-0.57	-0.61	26.76	7.43	0.00	15.51	0.00	0.00
597.00	819.00	56.68	4.25	1.20	0.00	0.17	1.89	0.09	7.57	29.14	23.00	0.00	37.00	-0.57	-0.61	36.46	0.00	0.06	20.79	-20.74	-1.44
598.00	819.00	60.95	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.14	23.00	0.00	37.00	-0.57	-0.61	24.67	8.52	0.00	14.32	0.00	0.00
599.00	819.00	68.03	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.29	23.00	0.00	38.00	-0.57	-0.61	27.05	7.08	0.00	15.60	0.00	0.00
600.00	819.00	75.02	6.99	1.20	0.00	0.17	1.89	0.09	7.57	29.29	23.00	0.00	38.00	-0.57	-0.61	28.52	0.00	51.70	16.42	35.28	1.72
601.00	819.00	78.12	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.29	23.00	0.00	38.00	-0.57	-0.61	21.48	10.08	0.00	12.52	0.00	0.00
602.00	819.00	83.73	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.29	23.00	0.00	38.00	-0.57	-0.61	29.03	5.62	0.00	16.64	0.00	0.00
603.00	819.00	91.43	7.70	1.20	0.00	0.17	1.89	0.09	7.57	29.43	23.00	0.00	39.00	-0.57	-0.61	27.71	0.00	42.60	15.96	26.64	1.22
604.00	819.00	91.95	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.43	23.00	0.00	39.00	-0.57	-0.61	26.42	8.22	0.00	15.25	0.00	0.00
605.00	819.00	100.27	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.43	23.00	0.00	39.00	-0.57	-0.61	24.96	8.32	0.00	14.45	0.00	0.00
606.00	819.00	108.57	0.00	1.20	50.00	0.17	1.89	0.09	7.57	29.43	23.00	0.00	39.00	-0.57	-0.61	24.33	8.30	0.00	14.09	0.00	0.00
607.00	819.00	115.02	6.45	1.20	0.00	0.17	1.89	0.09	7.57	29.57	23.00	0.00	40.00	-0.57	-0.61	28.46	0.00	35.50	16.35	19.15	0.71
608.00	823.00	0.00	0.00	1.63	80.00	0.59	1.13	0.52	1.33	34.29	28.00	1.00	44.00	-0.67	-1.44	0.00	0.00	0.00	0.00	0.00	0.00
609.00	823.00	7.32	0.00	1.76	80.00	0.62	1.22	0.51	1.36	34.29	28.00	1.00	44.00	-0.67	-1.44	1.79	7.32	0.00	2.90	0.00	0.00
610.00	823.00	15.28	0.00	1.97	80.00	0.68	1.37	0.50	1.40	34.43	28.00	1.00	45.00	-0.67	-1.44	1.32	7.97	0.00	2.75	0.00	0.00
611.00	823.00	23.23	0.00	2.02	80.00	0.69	1.40	0.49	1.41	34.43	28.00	1.00	45.00	-0.67	-1.44	1.32	7.95	0.00	2.75	0.00	0.00
612.00	823.00	31.43	0.00	2.09	80.00	0.71	1.45	0.49	1.42	34.43	28.00	1.00	45.00	-0.67	-1.44	1.17	8.20	0.00	2.56	0.00	0.00
613.00	823.00	39.22	0.00	2.20	80.00	1.10	1.52	0.72	0.96	34.57	28.00	1.00	46.00	-0.67	-1.44	0.23	7.78	0.00	1.15	0.00	0.00
614.00	823.00	47.05	0.00	2.40	80.00	1.18	1.66	0.71	0.98	34.57	28.00	1.00	46.00	-0.67	-1.44	0.23	7.83	0.00	1.02	0.00	0.00
615.00	823.00	55.88	0.00	2.46	80.00	1.20	1.71	0.70	0.99	34.57	28.00	1.00	46.00	-0.67	-1.44	0.11	8.83	0.00	0.72	0.00	0.00

616.00	823.00	63.25	0.00	2.51	80.00	1.22	1.74	0.70	0.99	34.71	28.00	1.00	47.00	-0.67	-1.44	0.32	7.37	0.00	1.13	0.00	0.00
617.00	823.00	114.82	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.00	28.00	1.00	49.00	-0.67	-1.44	0.00	51.57	0.00	0.00	0.00	0.00
618.00	823.00	121.90	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.00	28.00	1.00	49.00	-0.67	-1.44	0.78	7.08	0.00	2.35	0.00	0.00
619.00	823.00	129.77	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.14	28.00	1.00	50.00	-0.67	-1.44	0.45	7.87	0.00	2.00	0.00	0.00
620.00	823.00	130.90	1.13	2.51	0.00	1.22	1.74	0.70	0.99	35.14	28.00	1.00	50.00	-0.67	-1.44	50.16	0.00	125.00	17.82	107.18	4.89
621.00	823.00	138.07	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.14	28.00	1.00	50.00	-0.67	-1.44	0.33	8.30	0.00	1.71	0.00	0.00
622.00	823.00	145.58	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.14	28.00	1.00	50.00	-0.67	-1.44	0.58	7.52	0.00	2.19	0.00	0.00
623.00	823.00	153.35	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.29	28.00	1.00	51.00	-0.67	-1.44	0.48	7.77	0.00	2.05	0.00	0.00
624.00	823.00	159.48	6.13	2.51	0.00	1.22	1.74	0.70	0.99	35.29	28.00	1.00	51.00	-0.67	-1.44	1.52	0.00	0.04	3.49	-3.44	-0.86
625.00	823.00	161.82	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.29	28.00	1.00	51.00	-0.67	-1.44	0.30	8.47	0.00	1.62	0.00	0.00
626.00	823.00	169.67	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.29	28.00	1.00	51.00	-0.67	-1.44	0.46	7.85	0.00	1.95	0.00	0.00
627.00	823.00	177.57	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.43	28.00	1.00	52.00	-0.67	-1.44	0.44	7.90	0.00	1.95	0.00	0.00
628.00	823.00	186.07	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.43	28.00	1.00	52.00	-0.67	-1.44	0.29	8.50	0.00	1.60	0.00	0.00
629.00	823.00	193.92	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.43	28.00	1.00	52.00	-0.67	-1.44	0.46	7.85	0.00	1.95	0.00	0.00
630.00	823.00	201.55	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.57	28.00	1.00	53.00	-0.67	-1.44	0.53	7.63	0.00	2.13	0.00	0.00
631.00	823.00	205.48	3.93	2.51	0.00	1.22	1.74	0.70	0.99	35.57	28.00	1.00	53.00	-0.67	-1.44	7.08	0.00	3.62	7.17	-3.55	-0.91
632.00	823.00	209.68	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.57	28.00	1.00	53.00	-0.67	-1.44	0.38	8.13	0.00	1.82	0.00	0.00
633.00	823.00	218.07	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.57	28.00	1.00	53.00	-0.67	-1.44	0.31	8.38	0.00	1.65	0.00	0.00
634.00	823.00	225.28	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.71	28.00	1.00	54.00	-0.67	-1.44	0.71	7.22	0.00	2.41	0.00	0.00
635.00	823.00	228.48	3.20	2.51	0.00	1.22	1.74	0.70	0.99	35.71	28.00	1.00	54.00	-0.67	-1.44	11.82	0.00	3.59	9.21	-5.62	-1.16
636.00	823.00	232.98	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.71	28.00	1.00	54.00	-0.67	-1.44	0.51	7.70	0.00	2.12	0.00	0.00
637.00	823.00	240.83	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.71	28.00	1.00	54.00	-0.67	-1.44	0.46	7.85	0.00	1.99	0.00	0.00
638.00	823.00	249.98	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.86	28.00	1.00	55.00	-0.67	-1.44	0.18	9.15	0.00	1.30	0.00	0.00
639.00	823.00	256.68	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.86	28.00	1.00	55.00	-0.67	-1.44	1.02	6.70	0.00	2.81	0.00	0.00
640.00	823.00	265.23	0.00	2.51	160.00	1.22	1.74	0.70	0.99	35.86	28.00	1.00	55.00	-0.67	-1.44	0.28	8.55	0.00	1.63	0.00	0.00
641.00	823.00	274.50	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.00	28.00	1.00	56.00	-0.67	-1.44	0.17	9.27	0.00	1.23	0.00	0.00
642.00	823.00	276.73	2.23	2.51	0.00	1.22	1.74	0.70	0.99	36.00	28.00	1.00	56.00	-0.67	-1.44	23.18	0.00	14.70	12.07	2.63	-0.50
643.00	823.00	281.90	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.00	28.00	1.00	56.00	-0.67	-1.44	0.62	7.40	0.00	2.23	0.00	0.00
644.00	823.00	289.50	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.00	28.00	1.00	56.00	-0.67	-1.44	0.54	7.60	0.00	2.17	0.00	0.00
645.00	823.00	297.47	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.14	28.00	1.00	57.00	-0.67	-1.44	0.42	7.97	0.00	1.92	0.00	0.00



646.00	823.00	305.47	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.14	28.00	1.00	57.00	-0.67	-1.44	0.41	8.00	0.00	1.88	0.00	0.00
647.00	823.00	313.97	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.14	28.00	1.00	57.00	-0.67	-1.44	0.29	8.50	0.00	1.60	0.00	0.00
648.00	823.00	321.53	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.29	28.00	1.00	58.00	-0.67	-1.44	0.56	7.57	0.00	2.15	0.00	0.00
649.00	823.00	329.73	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.29	28.00	1.00	58.00	-0.67	-1.44	0.36	8.20	0.00	1.78	0.00	0.00
650.00	823.00	337.73	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.29	28.00	1.00	58.00	-0.67	-1.44	0.41	8.00	0.00	1.87	0.00	0.00
651.00	823.00	342.90	5.17	2.51	0.00	1.22	1.74	0.70	0.99	36.29	28.00	1.00	58.00	-0.67	-1.44	2.97	0.00	1.18	4.74	-3.56	-0.89
652.00	823.00	346.40	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.43	28.00	1.00	59.00	-0.67	-1.44	0.26	8.67	0.00	1.51	0.00	0.00
653.00	823.00	353.73	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.43	28.00	1.00	59.00	-0.67	-1.44	0.66	7.33	0.00	2.31	0.00	0.00
654.00	823.00	356.73	3.00	2.51	0.00	1.22	1.74	0.70	0.99	36.43	28.00	1.00	59.00	-0.67	-1.44	13.59	0.00	1.69	9.79	-8.10	-1.41
655.00	823.00	361.73	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.43	28.00	1.00	59.00	-0.67	-1.44	0.41	8.00	0.00	1.91	0.00	0.00
656.00	823.00	369.73	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.57	28.00	1.00	60.00	-0.67	-1.44	0.41	8.00	0.00	1.88	0.00	0.00
657.00	823.00	377.97	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.57	28.00	1.00	60.00	-0.67	-1.44	0.35	8.23	0.00	1.74	0.00	0.00
658.00	823.00	384.73	6.76	2.51	0.00	1.22	1.74	0.70	0.99	36.57	28.00	1.00	60.00	-0.67	-1.44	0.98	0.00	2.11	2.80	-0.69	0.07
659.00	823.00	385.22	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.57	28.00	1.00	60.00	-0.67	-1.44	0.69	7.25	0.00	2.39	0.00	0.00
660.00	823.00	393.43	0.00	2.51	160.00	1.22	1.74	0.70	0.99	36.71	28.00	1.00	61.00	-0.67	-1.44	0.36	8.22	0.00	1.79	0.00	0.00
661.00	823.00	396.98	3.55	2.51	0.00	1.22	1.74	0.70	0.99	36.71	28.00	1.00	61.00	-0.67	-1.44	9.23	0.00	5.27	8.02	-2.75	-0.84
662.00	824.00	0.00	0.00	1.39	121.00	0.17	2.10	0.08	8.81	28.00	25.00	0.00	21.00	-0.47	-0.65	0.00	0.00	0.00	0.00	0.00	0.00
663.00	824.00	11.67	0.00	1.39	121.00	0.17	2.10	0.08	8.81	28.14	25.00	0.00	22.00	-0.47	-0.65	23.41	11.67	0.00	14.18	0.00	0.00
664.00	824.00	23.33	0.00	1.29	121.00	0.16	1.95	0.08	8.65	28.14	25.00	0.00	22.00	-0.47	-0.65	34.73	11.67	0.00	22.11	0.00	0.00
665.00	824.00	36.00	0.00	1.29	121.00	0.16	1.95	0.08	8.65	28.29	25.00	0.00	23.00	-0.47	-0.65	35.47	12.67	0.00	23.62	0.00	0.00
666.00	824.00	47.83	0.00	1.29	121.00	0.16	1.95	0.08	8.65	28.29	25.00	0.00	23.00	-0.47	-0.65	38.23	11.83	0.00	25.66	0.00	0.00
667.00	824.00	50.50	2.67	1.22	0.00	0.15	1.85	0.08	8.53	28.29	25.00	0.00	23.00	-0.47	-0.65	86.35	0.00	24.85	51.59	-26.74	-0.55
668.00	824.00	56.33	8.50	1.22	0.00	0.15	1.85	0.08	8.53	28.29	25.00	0.00	23.00	-0.47	-0.65	53.76	0.00	38.70	34.81	3.89	0.07
669.00	824.00	59.50	0.00	1.22	121.00	0.15	1.85	0.08	8.53	28.43	25.00	0.00	24.00	-0.47	-0.65	41.55	11.67	0.00	28.11	0.00	0.00
670.00	824.00	63.33	3.83	1.22	0.00	0.15	1.85	0.08	8.53	28.43	25.00	0.00	24.00	-0.47	-0.65	79.40	0.00	205.50	48.46	157.04	3.14
671.00	824.00	71.33	0.00	1.22	121.00	0.15	1.85	0.08	8.53	28.43	25.00	0.00	24.00	-0.47	-0.65	41.44	11.83	0.00	28.25	0.00	0.00
672.00	824.00	73.67	2.34	1.22	0.00	0.15	1.85	0.08	8.53	28.43	25.00	0.00	24.00	-0.47	-0.65	89.53	0.00	10.60	53.70	-43.10	-0.83
673.00	824.00	79.75	8.42	1.22	0.00	0.15	1.85	0.08	8.53	28.43	25.00	0.00	24.00	-0.47	-0.65	54.62	0.00	0.15	35.63	-35.48	-1.05
674.00	824.00	95.00	0.00	1.22	121.00	0.15	1.85	0.08	8.53	28.57	25.00	0.00	25.00	-0.47	-0.65	15.82	23.67	0.00	12.74	0.00	0.00
675.00	824.00	98.25	3.25	1.22	0.00	0.15	1.85	0.08	8.53	28.57	25.00	0.00	25.00	-0.47	-0.65	63.47	0.00	5.63	38.05	-32.42	-0.88

676.00	830.00	0.00	0.00	1.61	100.80	2.69	8.61	0.31	2.22	39.57	30.00	2.00	65.00	0.40	0.61	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
678.00	830.00	5.17	0.00	1.67	100.80	2.77	8.94	0.31	2.24	39.57	30.00	2.00	65.00	0.40	0.61	2.46	5.17	0.00	3.19	0.00	0.00	0.00	0.00
679.00	830.00	11.33	0.00	1.67	100.80	2.77	8.94	0.31	2.24	39.71	30.00	2.00	66.00	0.40	0.61	2.18	6.17	0.00	2.49	0.00	0.00	0.00	0.00
680.00	830.00	15.25	3.92	1.67	0.00	2.77	8.94	0.31	2.24	39.71	30.00	2.00	66.00	0.40	0.61	4.27	0.00	0.64	5.69	-5.05	-0.73	-0.73	-0.73
681.00	830.00	16.50	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.71	30.00	2.00	66.00	0.40	0.61	2.53	5.17	0.00	3.10	0.00	0.00	0.00	0.00
682.00	830.00	22.67	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.71	30.00	2.00	66.00	0.40	0.61	2.07	6.17	0.00	2.36	0.00	0.00	0.00	0.00
683.00	830.00	24.50	1.83	1.94	0.00	3.09	10.38	0.30	2.32	39.71	30.00	2.00	66.00	0.40	0.61	7.27	0.00	3.65	11.22	-7.56	-0.48	-0.48	-0.48
684.00	830.00	29.07	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.71	30.00	2.00	66.00	0.40	0.61	1.86	6.40	0.00	2.10	0.00	0.00	0.00	0.00
685.00	830.00	35.33	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.86	30.00	2.00	67.00	0.40	0.61	1.91	6.27	0.00	2.18	0.00	0.00	0.00	0.00
687.00	830.00	39.25	3.92	1.94	0.00	3.09	10.38	0.30	2.32	39.86	30.00	2.00	67.00	0.40	0.61	3.85	0.00	7.48	5.17	2.31	0.67	0.67	0.67
688.00	830.00	40.83	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.86	30.00	2.00	67.00	0.40	0.61	2.40	5.50	0.00	2.89	0.00	0.00	0.00	0.00
689.00	830.00	47.25	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.86	30.00	2.00	67.00	0.40	0.61	1.90	6.42	0.00	2.13	0.00	0.00	0.00	0.00
690.00	830.00	53.08	0.00	1.94	100.80	3.09	10.38	0.30	2.32	39.86	30.00	2.00	67.00	0.40	0.61	2.18	5.83	0.00	2.56	0.00	0.00	0.00	0.00
691.00	830.00	59.83	0.00	1.94	100.80	3.09	10.38	0.30	2.32	40.00	30.00	2.00	68.00	0.40	0.61	1.69	6.75	0.00	1.86	0.00	0.00	0.00	0.00
692.00	830.00	64.90	0.00	1.94	100.80	3.09	10.38	0.30	2.32	40.00	30.00	2.00	68.00	0.40	0.61	2.68	5.07	0.00	3.34	0.00	0.00	0.00	0.00
693.00	830.00	71.42	0.00	1.94	100.80	3.09	10.38	0.30	2.32	40.00	30.00	2.00	68.00	0.40	0.61	1.88	6.52	0.00	2.10	0.00	0.00	0.00	0.00
694.00	830.00	76.70	0.00	1.94	100.80	3.09	10.38	0.30	2.32	40.00	30.00	2.00	68.00	0.40	0.61	2.56	5.28	0.00	3.13	0.00	0.00	0.00	0.00
695.00	830.00	83.17	0.00	1.94	100.80	3.09	10.38	0.30	2.32	40.14	30.00	2.00	69.00	0.40	0.61	1.89	6.47	0.00	2.12	0.00	0.00	0.00	0.00
696.00	830.00	88.50	0.00	1.94	100.80	3.09	10.38	0.30	2.32	40.14	30.00	2.00	69.00	0.40	0.61	2.52	5.33	0.00	3.07	0.00	0.00	0.00	0.00
698.00	837.00	0.00	0.00	1.89	180.00	0.39	2.57	0.15	4.52	35.71	32.00	2.00	24.00	-0.87	-0.76	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
699.00	837.00	7.33	0.00	1.86	180.00	0.39	2.53	0.15	4.50	35.71	32.00	2.00	24.00	-0.87	-0.76	23.96	7.33	0.00	9.85	0.00	0.00	0.00	0.00
700.00	837.00	15.33	0.00	1.86	180.00	0.39	2.53	0.15	4.50	35.71	32.00	2.00	24.00	-0.87	-0.76	28.59	8.00	0.00	11.27	0.00	0.00	0.00	0.00
701.00	837.00	18.63	3.30	2.01	0.00	0.41	2.73	0.15	4.59	35.71	32.00	2.00	24.00	-0.87	-0.76	57.68	0.00	71.70	24.38	47.32	1.05	1.05	1.05
702.00	837.00	23.65	0.00	2.01	180.00	0.41	2.73	0.15	4.59	35.86	32.00	2.00	25.00	-0.87	-0.76	27.02	8.32	0.00	10.47	0.00	0.00	0.00	0.00
703.00	837.00	24.50	0.85	2.01	0.00	0.41	2.73	0.15	4.59	35.86	32.00	2.00	25.00	-0.87	-0.76	84.01	0.00	6.12	36.87	-30.75	-1.45	-1.45	-1.45
704.00	837.00	31.33	0.00	2.01	180.00	0.41	2.73	0.15	4.59	35.86	32.00	2.00	25.00	-0.87	-0.76	29.94	7.68	0.00	11.67	0.00	0.00	0.00	0.00
705.00	837.00	38.65	7.32	2.01	0.00	0.41	2.73	0.15	4.59	35.86	32.00	2.00	25.00	-0.87	-0.76	32.58	0.00	59.80	12.75	47.05	2.62	2.62	2.62
706.00	837.00	39.33	0.00	2.01	180.00	0.41	2.73	0.15	4.59	35.86	32.00	2.00	25.00	-0.87	-0.76	29.40	8.00	0.00	11.37	0.00	0.00	0.00	0.00
707.00	837.00	47.70	0.00	2.01	180.00	0.41	2.73	0.15	4.59	36.00	32.00	2.00	26.00	-0.87	-0.76	27.65	8.37	0.00	10.61	0.00	0.00	0.00	0.00
708.00	837.00	52.08	4.38	2.01	0.00	0.41	2.73	0.15	4.59	36.00	32.00	2.00	26.00	-0.87	-0.76	49.61	0.00	80.00	20.41	59.59	1.98	1.98	1.98

709.00	837.00	55.67	0.00	2.01	180.00	0.41	2.73	0.15	4.59	36.00	32.00	2.00	26.00	-0.87	-0.76	28.84	7.97	0.00	11.15	0.00	0.00
710.00	837.00	61.17	5.50	2.01	0.00	0.41	2.73	0.15	4.59	36.00	32.00	2.00	26.00	-0.87	-0.76	42.41	0.00	63.70	17.12	46.59	1.72
711.00	840.00	0.00	0.00	1.71	80.00	0.25	1.47	0.17	4.10	32.29	28.00	2.00	30.00	-1.06	-1.22	0.00	0.00	0.00	0.00	0.00	0.00
712.00	840.00	8.33	0.00	1.85	80.00	0.26	1.59	0.17	4.18	32.29	28.00	2.00	30.00	-1.06	-1.22	13.21	8.33	0.00	4.75	0.00	0.00
713.00	840.00	16.63	0.00	2.01	80.00	0.28	1.72	0.16	4.27	32.29	28.00	2.00	30.00	-1.06	-1.22	15.72	8.30	0.00	5.89	0.00	0.00
714.00	840.00	24.50	0.00	2.19	80.00	0.30	1.88	0.16	4.36	32.43	28.00	2.00	31.00	-1.06	-1.22	16.84	7.87	0.00	6.35	0.00	0.00
715.00	840.00	32.32	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.43	28.00	2.00	31.00	-1.06	-1.22	17.31	7.82	0.00	6.58	0.00	0.00
716.00	840.00	40.83	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.43	28.00	2.00	31.00	-1.06	-1.22	15.77	8.52	0.00	6.12	0.00	0.00
717.00	840.00	46.50	5.67	2.25	0.00	0.30	1.93	0.16	4.39	32.57	28.00	2.00	32.00	-1.06	-1.22	24.07	0.00	45.10	8.76	36.34	2.66
718.00	840.00	48.45	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.57	28.00	2.00	32.00	-1.06	-1.22	17.69	7.62	0.00	6.74	0.00	0.00
719.00	840.00	56.47	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.57	28.00	2.00	32.00	-1.06	-1.22	17.15	8.02	0.00	6.60	0.00	0.00
720.00	840.00	64.80	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.57	28.00	2.00	32.00	-1.06	-1.22	16.18	8.33	0.00	6.28	0.00	0.00
721.00	840.00	72.55	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.71	28.00	2.00	33.00	-1.06	-1.22	17.45	7.75	0.00	6.68	0.00	0.00
722.00	840.00	80.80	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.71	28.00	2.00	33.00	-1.06	-1.22	16.47	8.25	0.00	6.37	0.00	0.00
723.00	840.00	88.85	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.71	28.00	2.00	33.00	-1.06	-1.22	16.73	8.05	0.00	6.45	0.00	0.00
724.00	840.00	94.33	5.48	2.25	0.00	0.30	1.93	0.16	4.39	32.86	28.00	2.00	34.00	-1.06	-1.22	25.20	0.00	31.30	9.14	22.16	0.92
725.00	840.00	96.73	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.86	28.00	2.00	34.00	-1.06	-1.22	17.25	7.88	0.00	6.62	0.00	0.00
726.00	840.00	104.25	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.86	28.00	2.00	34.00	-1.06	-1.22	18.42	7.52	0.00	7.01	0.00	0.00
727.00	840.00	112.90	0.00	2.25	80.00	0.30	1.93	0.16	4.39	32.86	28.00	2.00	34.00	-1.06	-1.22	15.71	8.65	0.00	6.15	0.00	0.00
728.00	840.00	120.63	0.00	2.25	80.00	0.30	1.93	0.16	4.39	33.00	28.00	2.00	35.00	-1.06	-1.22	17.37	7.73	0.00	6.65	0.00	0.00
729.00	840.00	128.62	0.00	2.25	80.00	0.30	1.93	0.16	4.39	33.00	28.00	2.00	35.00	-1.06	-1.22	17.14	7.98	0.00	6.59	0.00	0.00
730.00	840.00	136.93	0.00	2.25	80.00	0.30	1.93	0.16	4.39	33.00	28.00	2.00	35.00	-1.06	-1.22	16.23	8.32	0.00	6.30	0.00	0.00
731.00	840.00	142.42	5.49	2.25	0.00	0.30	1.93	0.16	4.39	33.14	28.00	2.00	36.00	-1.06	-1.22	24.95	0.00	34.70	9.05	25.65	1.33
732.00	840.00	144.68	0.00	2.25	80.00	0.30	1.93	0.16	4.39	33.14	28.00	2.00	36.00	-1.06	-1.22	17.47	7.75	0.00	6.68	0.00	0.00
733.00	840.00	153.72	0.00	2.25	80.00	0.30	1.93	0.16	4.39	33.14	28.00	2.00	36.00	-1.06	-1.22	14.55	9.03	0.00	5.73	0.00	0.00
734.00	840.00	161.40	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.14	28.00	2.00	36.00	-1.06	-1.22	17.16	7.68	0.00	6.55	0.00	0.00
735.00	840.00	168.82	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.29	28.00	2.00	37.00	-1.06	-1.22	22.03	7.42	0.00	8.24	0.00	0.00
736.00	840.00	176.57	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.29	28.00	2.00	37.00	-1.06	-1.22	22.34	7.75	0.00	8.49	0.00	0.00
737.00	840.00	184.80	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.29	28.00	2.00	37.00	-1.06	-1.22	20.80	8.23	0.00	8.04	0.00	0.00
738.00	840.00	193.03	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.43	28.00	2.00	38.00	-1.06	-1.22	20.38	8.23	0.00	7.89	0.00	0.00

739.00	840.00	199.98	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.43	28.00	2.00	38.00	-1.06	-1.22	24.80	6.95	0.00	9.31	0.00	0.00
740.00	840.00	208.87	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.43	28.00	2.00	38.00	-1.06	-1.22	19.35	8.88	0.00	7.60	0.00	0.00
741.00	840.00	216.82	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.57	28.00	2.00	39.00	-1.06	-1.22	20.88	7.95	0.00	8.04	0.00	0.00
743.00	840.00	225.45	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.57	28.00	2.00	39.00	-1.06	-1.22	19.15	8.63	0.00	7.48	0.00	0.00
744.00	840.00	231.95	0.00	2.25	100.00	0.30	1.93	0.16	4.39	33.57	28.00	2.00	39.00	-1.06	-1.22	26.19	6.50	0.00	9.72	0.00	0.00
745.00	840.00	238.83	6.88	2.25	0.00	0.30	1.93	0.16	4.39	33.71	28.00	2.00	40.00	-1.06	-1.22	27.04	0.00	36.00	10.12	25.88	1.15
780.00	1156.00	0.00	0.00	0.99	75.00	1.29	16.99	0.08	9.13	29.71	24.00	0.00	34.00	1.33	1.77	0.00	0.00	0.00	0.00	0.00	0.00
781.00	1156.00	8.10	0.00	1.00	75.00	1.30	17.16	0.08	9.15	29.71	24.00	0.00	34.00	1.33	1.77	2.41	8.10	0.00	10.24	0.00	0.00
782.00	1156.00	15.92	0.00	1.00	75.00	1.30	17.16	0.08	9.15	29.86	24.00	0.00	35.00	1.33	1.77	3.80	7.82	0.00	14.67	0.00	0.00
783.00	1156.00	16.38	0.46	1.00	0.00	1.30	17.16	0.08	9.15	29.86	24.00	0.00	35.00	1.33	1.77	7.62	0.00	5.10	36.96	-31.86	-0.58
784.00	1178.00	0.00	0.00	0.67	47.00	0.48	7.31	0.07	10.46	28.29	25.00	0.00	23.00	1.10	1.33	0.00	0.00	0.00	0.00	0.00	0.00
785.00	1178.00	2.33	2.33	0.67	0.00	0.48	7.31	0.07	10.46	28.29	25.00	0.00	23.00	1.10	1.33	5.60	0.00	9.65	20.37	-10.72	-0.14
786.00	1178.00	11.38	0.00	0.67	47.00	0.59	7.31	0.08	8.56	28.29	25.00	0.00	23.00	1.10	1.33	2.69	11.38	0.00	8.16	0.00	0.00
787.00	1178.00	15.92	4.54	0.67	0.00	0.59	7.31	0.08	8.56	28.29	25.00	0.00	23.00	1.10	1.33	6.40	0.00	4.17	20.84	-16.67	-0.45
788.00	1178.00	23.90	0.00	0.67	47.00	0.59	7.31	0.08	8.56	28.43	25.00	0.00	24.00	1.10	1.33	3.36	12.52	0.00	9.30	0.00	0.00
789.00	1178.00	27.00	3.10	0.67	0.00	0.59	7.31	0.08	8.56	28.43	25.00	0.00	24.00	1.10	1.33	7.71	0.00	6.65	24.94	-18.29	-0.41
798.00	1186.00	0.00	0.00	1.13	75.00	0.23	1.37	0.16	4.22	29.43	26.00	1.00	21.00	-0.51	-0.88	0.00	0.00	0.00	0.00	0.00	0.00
799.00	1186.00	1.45	1.45	1.13	0.00	0.23	1.37	0.16	4.22	29.43	26.00	1.00	21.00	-0.51	-0.88	44.88	0.00	27.00	19.85	7.15	-0.33
800.00	1186.00	1.58	1.58	1.13	0.00	0.23	1.37	0.16	4.22	29.43	26.00	1.00	21.00	-0.51	-0.88	43.93	0.00	91.70	19.56	72.14	2.64
801.00	1186.00	9.55	0.00	1.13	75.00	0.23	1.37	0.16	4.22	29.57	26.00	1.00	22.00	-0.51	-0.88	11.87	9.55	0.00	7.89	0.00	0.00
802.00	1186.00	14.95	5.40	1.13	0.00	0.23	1.37	0.16	4.22	29.57	26.00	1.00	22.00	-0.51	-0.88	28.36	0.00	16.45	16.92	-0.47	-0.63
854.00	6100.00	0.00	0.00	0.85	42.00	0.32	9.48	0.03	20.27	28.00	26.00	1.00	13.00	1.12	1.35	0.00	0.00	0.00	0.00	0.00	0.00
855.00	6100.00	8.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.00	26.00	1.00	13.00	1.12	1.35	3.44	8.00	0.00	12.28	0.00	0.00
856.00	6100.00	16.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.00	26.00	1.00	13.00	1.12	1.35	6.01	8.00	0.00	20.82	0.00	0.00
857.00	6100.00	24.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.14	26.00	1.00	14.00	1.12	1.35	7.93	8.00	0.00	26.76	0.00	0.00
858.00	6100.00	32.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.14	26.00	1.00	14.00	1.12	1.35	9.37	8.00	0.00	30.89	0.00	0.00
859.00	6100.00	40.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.14	26.00	1.00	14.00	1.12	1.35	10.45	8.00	0.00	33.76	0.00	0.00
860.00	6100.00	48.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.29	26.00	1.00	15.00	1.12	1.35	11.26	8.00	0.00	35.76	0.00	0.00
861.00	6100.00	56.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.29	26.00	1.00	15.00	1.12	1.35	11.86	8.00	0.00	37.15	0.00	0.00
862.00	6100.00	64.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.29	26.00	1.00	15.00	1.12	1.35	12.31	8.00	0.00	38.12	0.00	0.00

863.00	6100.00	72.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.43	26.00	1.00	16.00	1.12	1.35	12.65	8.00	0.00	38.79	0.00	0.00
864.00	6100.00	80.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.43	26.00	1.00	16.00	1.12	1.35	12.90	8.00	0.00	39.25	0.00	0.00
865.00	6100.00	88.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.43	26.00	1.00	16.00	1.12	1.35	13.09	8.00	0.00	39.58	0.00	0.00
866.00	6100.00	96.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.57	26.00	1.00	17.00	1.12	1.35	13.23	8.00	0.00	39.80	0.00	0.00
867.00	6100.00	104.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.57	26.00	1.00	17.00	1.12	1.35	13.34	8.00	0.00	39.96	0.00	0.00
868.00	6100.00	112.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.57	26.00	1.00	17.00	1.12	1.35	13.42	8.00	0.00	40.07	0.00	0.00
869.00	6100.00	120.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.71	26.00	1.00	18.00	1.12	1.35	13.48	8.00	0.00	40.15	0.00	0.00
870.00	6100.00	128.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.71	26.00	1.00	18.00	1.12	1.35	13.52	8.00	0.00	40.20	0.00	0.00
871.00	6100.00	136.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.71	26.00	1.00	18.00	1.12	1.35	13.56	8.00	0.00	40.24	0.00	0.00
872.00	6100.00	144.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.86	26.00	1.00	19.00	1.12	1.35	13.58	8.00	0.00	40.26	0.00	0.00
873.00	6100.00	152.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.86	26.00	1.00	19.00	1.12	1.35	13.60	8.00	0.00	40.28	0.00	0.00
874.00	6100.00	160.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	28.86	26.00	1.00	19.00	1.12	1.35	13.61	8.00	0.00	40.29	0.00	0.00
875.00	6100.00	168.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	29.00	26.00	1.00	20.00	1.12	1.35	13.63	8.00	0.00	40.30	0.00	0.00
876.00	6100.00	176.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	29.00	26.00	1.00	20.00	1.12	1.35	13.63	8.00	0.00	40.31	0.00	0.00
877.00	6100.00	184.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	29.00	26.00	1.00	20.00	1.12	1.35	13.64	8.00	0.00	40.31	0.00	0.00
878.00	6100.00	192.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	29.14	26.00	1.00	21.00	1.12	1.35	13.64	8.00	0.00	40.31	0.00	0.00
880.00	6100.00	203.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	29.14	26.00	1.00	21.00	1.12	1.35	12.24	11.00	0.00	35.18	0.00	0.00
881.00	6100.00	211.00	0.00	0.83	42.00	0.33	9.23	0.04	19.13	29.14	26.00	1.00	21.00	1.12	1.35	12.60	8.00	0.00	36.75	0.00	0.00
882.00	6100.00	217.33	6.33	0.83	0.00	0.33	9.23	0.04	19.13	29.29	26.00	1.00	22.00	1.12	1.35	13.67	0.00	9.90	40.82	-30.92	-0.57
883.00	6104.00	0.00	0.00	0.40	20.00	0.24	2.90	0.08	8.39	26.29	25.00	0.00	7.00	0.69	0.91	0.00	0.00	0.00	0.00	0.00	0.00
884.00	6104.00	8.00	0.00	0.40	20.00	0.20	2.90	0.07	10.07	26.29	25.00	0.00	7.00	0.69	0.91	4.05	8.00	0.00	8.81	0.00	0.00
885.00	6104.00	12.72	4.72	0.40	0.00	0.20	2.90	0.07	10.07	26.43	25.00	0.00	8.00	0.69	0.91	7.99	0.00	5.95	17.54	-11.59	-0.45
886.00	6104.00	14.33	6.33	0.40	0.00	0.20	2.90	0.07	10.07	26.43	25.00	0.00	8.00	0.69	0.91	7.15	0.00	11.20	15.27	-4.07	-0.07
919.00	6109.00	0.00	0.00	0.67	61.00	0.49	3.45	0.14	4.88	29.57	26.00	1.00	20.00	0.50	0.57	0.00	0.00	0.00	0.00	0.00	0.00
920.00	6109.00	8.00	0.00	0.72	61.00	0.44	3.69	0.12	5.79	29.57	26.00	1.00	20.00	0.50	0.57	6.54	8.00	0.00	10.84	0.00	0.00
921.00	6109.00	16.00	0.00	0.72	61.00	0.44	3.69	0.12	5.79	29.71	26.00	1.00	21.00	0.50	0.57	9.04	8.00	0.00	14.75	0.00	0.00
922.00	6109.00	23.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	29.71	26.00	1.00	21.00	0.50	0.57	11.38	7.00	0.00	18.51	0.00	0.00
923.00	6109.00	31.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	29.71	26.00	1.00	21.00	0.50	0.57	10.95	8.00	0.00	17.58	0.00	0.00
924.00	6109.00	38.00	7.00	0.71	0.00	0.44	3.65	0.12	5.78	29.86	26.00	1.00	22.00	0.50	0.57	12.16	0.00	4.08	19.60	-15.53	-0.67
925.00	6109.00	39.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	29.86	26.00	1.00	22.00	0.50	0.57	10.79	8.00	0.00	17.25	0.00	0.00

926.00	6109.00	47.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	29.86	26.00	1.00	22.00	0.50	0.57	10.72	8.00	0.00	17.13	0.00	0.00
927.00	6109.00	55.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	29.86	26.00	1.00	22.00	0.50	0.57	10.70	8.00	0.00	17.08	0.00	0.00
928.00	6109.00	61.45	6.45	0.71	0.00	0.44	3.65	0.12	5.78	30.00	26.00	1.00	23.00	0.50	0.57	12.87	0.00	21.35	20.81	0.54	0.17
929.00	6109.00	63.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	30.00	26.00	1.00	23.00	0.50	0.57	10.69	8.00	0.00	17.07	0.00	0.00
930.00	6109.00	71.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	30.00	26.00	1.00	23.00	0.50	0.57	10.69	8.00	0.00	17.06	0.00	0.00
932.00	6109.00	79.00	0.00	0.71	61.00	0.44	3.65	0.12	5.78	30.00	26.00	1.00	23.00	0.50	0.57	10.68	8.00	0.00	17.06	0.00	0.00
933.00	6109.00	85.50	6.50	0.71	0.00	0.44	3.65	0.12	5.78	30.14	26.00	1.00	24.00	0.50	0.57	12.79	0.00	16.74	20.67	-3.93	-0.05
934.00	6118.00	0.00	0.00	0.64	45.00	0.08	1.31	0.06	11.27	28.14	23.00	0.00	32.00	-0.28	-0.35	0.00	0.00	0.00	0.00	0.00	0.00
935.00	6118.00	6.00	0.00	0.64	45.00	0.09	1.31	0.07	10.57	28.14	23.00	0.00	32.00	-0.28	-0.35	23.56	6.00	0.00	17.05	0.00	0.00
936.00	6118.00	12.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.14	23.00	0.00	32.00	-0.28	-0.35	37.19	6.00	0.00	27.29	0.00	0.00
937.00	6118.00	18.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.14	23.00	0.00	32.00	-0.28	-0.35	45.85	6.00	0.00	33.99	0.00	0.00
938.00	6118.00	24.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.29	23.00	0.00	33.00	-0.28	-0.35	51.35	6.00	0.00	38.37	0.00	0.00
939.00	6118.00	30.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.29	23.00	0.00	33.00	-0.28	-0.35	54.84	6.00	0.00	41.23	0.00	0.00
940.00	6118.00	36.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.29	23.00	0.00	33.00	-0.28	-0.35	57.06	6.00	0.00	43.10	0.00	0.00
941.00	6118.00	42.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.29	23.00	0.00	33.00	-0.28	-0.35	58.46	6.00	0.00	44.33	0.00	0.00
942.00	6118.00	48.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.43	23.00	0.00	34.00	-0.28	-0.35	59.36	6.00	0.00	45.13	0.00	0.00
943.00	6118.00	54.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.43	23.00	0.00	34.00	-0.28	-0.35	59.92	6.00	0.00	45.65	0.00	0.00
944.00	6118.00	60.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.43	23.00	0.00	34.00	-0.28	-0.35	60.28	6.00	0.00	45.99	0.00	0.00
945.00	6118.00	68.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.57	23.00	0.00	35.00	-0.28	-0.35	52.01	8.00	0.00	40.11	0.00	0.00
947.00	6118.00	73.00	0.00	0.64	45.00	0.10	1.31	0.08	9.16	28.57	23.00	0.00	35.00	-0.28	-0.35	59.61	5.00	0.00	45.48	0.00	0.00
948.00	6118.00	75.67	2.67	0.64	0.00	0.10	1.31	0.08	9.16	28.57	23.00	0.00	35.00	-0.28	-0.35	77.30	0.00	115.00	58.09	56.92	0.71
949.00	6126.00	0.00	0.00	0.68	50.00	0.08	1.78	0.05	14.62	27.57	26.00	1.00	8.00	-0.11	-0.10	0.00	0.00	0.00	0.00	0.00	0.00
950.00	6126.00	8.00	0.00	0.76	50.00	0.08	1.98	0.04	16.61	27.71	26.00	1.00	9.00	-0.11	-0.10	18.25	8.00	0.00	16.42	0.00	0.00
951.00	6126.00	16.00	0.00	0.79	50.00	0.09	2.08	0.05	15.20	27.71	26.00	1.00	9.00	-0.11	-0.10	29.00	8.00	0.00	26.07	0.00	0.00
952.00	6126.00	24.00	0.00	0.69	50.00	0.09	1.81	0.05	13.91	27.71	26.00	1.00	9.00	-0.11	-0.10	41.18	8.00	0.00	36.98	0.00	0.00
953.00	6126.00	31.33	7.33	0.69	0.00	0.10	1.82	0.05	13.16	27.86	26.00	1.00	10.00	-0.11	-0.10	46.71	0.00	61.70	41.91	19.79	0.21
954.00	6126.00	32.00	0.00	0.69	50.00	0.10	1.82	0.05	13.16	27.86	26.00	1.00	10.00	-0.11	-0.10	45.09	8.00	0.00	40.45	0.00	0.00
955.00	6126.00	39.00	0.00	0.69	50.00	0.10	1.82	0.06	12.39	27.86	26.00	1.00	10.00	-0.11	-0.10	49.31	7.00	0.00	44.20	0.00	0.00
956.00	6126.00	49.00	0.00	0.69	50.00	0.10	1.82	0.06	12.39	27.86	26.00	1.00	10.00	-0.11	-0.10	44.10	10.00	0.00	39.47	0.00	0.00
957.00	6126.00	55.58	6.58	0.69	0.00	0.12	1.82	0.06	10.84	28.00	26.00	1.00	11.00	-0.11	-0.10	47.28	0.00	94.10	42.32	51.78	0.99

958.00	6126.00	57.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.00	26.00	1.00	11.00	-0.11	-0.10	43.17	8.00	0.00	38.62	0.00	0.00
959.00	6126.00	63.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.00	26.00	1.00	11.00	-0.11	-0.10	48.43	6.00	0.00	43.36	0.00	0.00
960.00	6126.00	73.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.00	26.00	1.00	11.00	-0.11	-0.10	40.28	10.00	0.00	36.00	0.00	0.00
961.00	6126.00	79.33	6.33	0.69	0.00	0.13	1.82	0.07	10.06	28.14	26.00	1.00	12.00	-0.11	-0.10	44.12	0.00	86.70	39.46	47.24	0.98
962.00	6126.00	81.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.14	26.00	1.00	12.00	-0.11	-0.10	39.65	8.00	0.00	35.44	0.00	0.00
963.00	6126.00	87.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.14	26.00	1.00	12.00	-0.11	-0.10	46.03	6.00	0.00	41.19	0.00	0.00
964.00	6126.00	97.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.14	26.00	1.00	12.00	-0.11	-0.10	39.01	10.00	0.00	34.86	0.00	0.00
965.00	6126.00	103.08	6.08	0.69	0.00	0.12	1.82	0.06	10.84	28.29	26.00	1.00	13.00	-0.11	-0.10	45.37	0.00	39.70	40.59	-0.89	-0.27
966.00	6126.00	105.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.29	26.00	1.00	13.00	-0.11	-0.10	40.12	8.00	0.00	35.87	0.00	0.00
967.00	6126.00	111.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.29	26.00	1.00	13.00	-0.11	-0.10	46.36	6.00	0.00	41.49	0.00	0.00
968.00	6126.00	121.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.29	26.00	1.00	13.00	-0.11	-0.10	39.18	10.00	0.00	35.02	0.00	0.00
969.00	6126.00	127.17	6.17	0.69	0.00	0.12	1.82	0.06	10.84	28.43	26.00	1.00	14.00	-0.11	-0.10	45.22	0.00	30.60	40.46	-9.86	-0.49
970.00	6126.00	129.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.43	26.00	1.00	14.00	-0.11	-0.10	40.23	8.00	0.00	35.96	0.00	0.00
971.00	6126.00	135.00	0.00	0.69	50.00	0.12	1.82	0.06	10.84	28.43	26.00	1.00	14.00	-0.11	-0.10	46.43	6.00	0.00	41.55	0.00	0.00
972.00	6126.00	140.25	5.25	0.69	0.00	0.12	1.82	0.06	10.84	28.43	26.00	1.00	14.00	-0.11	-0.10	53.14	0.00	46.70	47.59	-0.89	-0.25
973.00	6126.00	142.50	7.50	0.69	0.00	0.12	1.82	0.06	10.84	28.43	26.00	1.00	14.00	-0.11	-0.10	46.02	0.00	48.30	41.17	7.13	-0.07
974.00	6130.00	0.00	0.00	1.17	120.00	0.12	0.92	0.13	5.47	33.71	24.00	0.00	62.00	-1.06	-1.31	0.00	0.00	0.00	0.00	0.00	0.00
975.00	6130.00	5.83	5.83	1.17	0.00	0.09	0.92	0.10	6.84	33.86	24.00	0.00	63.00	-1.06	-1.31	74.27	0.00	108.00	22.64	85.36	1.91
976.00	6130.00	7.50	0.00	1.17	120.00	0.10	0.92	0.11	6.15	33.86	24.00	0.00	63.00	-1.06	-1.31	61.53	7.50	0.00	19.55	0.00	0.00
977.00	6130.00	13.50	0.00	1.17	120.00	0.09	0.92	0.10	6.84	33.86	24.00	0.00	63.00	-1.06	-1.31	106.49	6.00	0.00	34.50	0.00	0.00
978.00	6130.00	21.50	0.00	1.17	120.00	0.09	0.92	0.10	6.84	33.86	24.00	0.00	63.00	-1.06	-1.31	106.93	8.00	0.00	37.40	0.00	0.00
979.00	6130.00	23.25	1.75	1.17	0.00	0.09	0.92	0.10	6.84	33.86	24.00	0.00	63.00	-1.06	-1.31	201.85	0.00	105.00	63.82	41.18	-0.53
980.00	6130.00	29.50	0.00	1.17	120.00	0.09	0.92	0.10	6.84	34.00	24.00	0.00	64.00	-1.06	-1.31	107.12	8.00	0.00	38.94	0.00	0.00
981.00	6130.00	34.17	4.67	1.27	0.00	0.14	0.99	0.14	4.88	34.00	24.00	0.00	64.00	-1.06	-1.31	115.61	0.00	306.00	41.42	264.58	5.14
982.00	6130.00	37.50	0.00	1.27	120.00	0.16	0.99	0.17	4.18	34.00	24.00	0.00	64.00	-1.06	-1.31	66.59	8.00	0.00	26.94	0.00	0.00
984.00	6130.00	45.50	0.00	1.27	120.00	0.16	0.99	0.17	4.18	34.00	24.00	0.00	64.00	-1.06	-1.31	51.18	8.00	0.00	21.54	0.00	0.00
985.00	6130.00	49.83	4.33	1.27	0.00	0.16	0.99	0.17	4.18	34.00	24.00	0.00	64.00	-1.06	-1.31	86.50	0.00	85.00	31.52	53.48	0.35
986.00	6130.00	53.50	0.00	1.27	120.00	0.16	0.99	0.17	4.18	34.14	24.00	0.00	65.00	-1.06	-1.31	47.09	8.00	0.00	19.62	0.00	0.00
987.00	6130.00	57.58	4.08	1.27	0.00	0.16	0.99	0.17	4.18	34.14	24.00	0.00	65.00	-1.06	-1.31	88.08	0.00	94.00	31.42	62.58	0.62
988.00	6130.00	61.50	0.00	1.27	120.00	0.16	0.99	0.17	4.18	34.14	24.00	0.00	65.00	-1.06	-1.31	46.01	8.00	0.00	18.93	0.00	0.00

991.00	6130.00	67.75	6.25	1.27	0.00	0.16	0.99	0.17	4.18	34.14	24.00	0.00	65.00	-1.06	-1.31	61.09	0.00	14.80	23.44	-8.63	-1.80
992.00	6130.00	69.50	8.00	1.27	0.00	0.16	0.99	0.17	4.18	34.14	24.00	0.00	65.00	-1.06	-1.31	45.72	0.00	37.90	18.69	19.21	-0.32
993.00	6134.00	0.00	0.00	0.52	50.00	0.27	3.27	0.08	8.44	24.43	24.00	0.00	1.00	0.61	0.77	0.00	0.00	0.00	0.00	0.00	0.00
994.00	6134.00	8.00	0.00	0.51	50.00	0.26	3.19	0.08	8.39	24.57	24.00	0.00	2.00	0.61	0.77	8.26	8.00	0.00	15.91	0.00	0.00
995.00	6134.00	16.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.57	24.00	0.00	2.00	0.61	0.77	12.60	8.00	0.00	23.36	0.00	0.00
996.00	6134.00	24.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.57	24.00	0.00	2.00	0.61	0.77	14.81	8.00	0.00	26.71	0.00	0.00
997.00	6134.00	36.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.71	24.00	0.00	3.00	0.61	0.77	11.45	12.00	0.00	19.11	0.00	0.00
998.00	6134.00	44.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.71	24.00	0.00	3.00	0.61	0.77	14.22	8.00	0.00	24.76	0.00	0.00
999.00	6134.00	52.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.71	24.00	0.00	3.00	0.61	0.77	15.64	8.00	0.00	27.35	0.00	0.00
1000.00	6134.00	60.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.86	24.00	0.00	4.00	0.61	0.77	16.38	8.00	0.00	28.54	0.00	0.00
1001.00	6134.00	68.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.86	24.00	0.00	4.00	0.61	0.77	16.75	8.00	0.00	29.08	0.00	0.00
1002.00	6134.00	76.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	24.86	24.00	0.00	4.00	0.61	0.77	16.95	8.00	0.00	29.33	0.00	0.00
1003.00	6134.00	84.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.00	24.00	0.00	5.00	0.61	0.77	17.05	8.00	0.00	29.44	0.00	0.00
1004.00	6134.00	92.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.00	24.00	0.00	5.00	0.61	0.77	17.10	8.00	0.00	29.49	0.00	0.00
1005.00	6134.00	100.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.00	24.00	0.00	5.00	0.61	0.77	17.13	8.00	0.00	29.52	0.00	0.00
1006.00	6134.00	108.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.14	24.00	0.00	6.00	0.61	0.77	17.14	8.00	0.00	29.53	0.00	0.00
1007.00	6134.00	116.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.14	24.00	0.00	6.00	0.61	0.77	17.15	8.00	0.00	29.53	0.00	0.00
1008.00	6134.00	124.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.14	24.00	0.00	6.00	0.61	0.77	17.15	8.00	0.00	29.54	0.00	0.00
1009.00	6134.00	132.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.29	24.00	0.00	7.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1010.00	6134.00	140.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.29	24.00	0.00	7.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1011.00	6134.00	148.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.29	24.00	0.00	7.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1012.00	6134.00	156.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.43	24.00	0.00	8.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1013.00	6134.00	164.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.43	24.00	0.00	8.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1014.00	6134.00	172.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.43	24.00	0.00	8.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1015.00	6134.00	180.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.57	24.00	0.00	9.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1016.00	6134.00	188.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.57	24.00	0.00	9.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1017.00	6134.00	196.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.57	24.00	0.00	9.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1018.00	6134.00	204.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.71	24.00	0.00	10.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1019.00	6134.00	212.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.71	24.00	0.00	10.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1020.00	6134.00	220.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.71	24.00	0.00	10.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00



1021.00	6134.00	228.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.86	24.00	0.00	11.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1022.00	6134.00	236.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.86	24.00	0.00	11.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1023.00	6134.00	244.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	25.86	24.00	0.00	11.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1024.00	6134.00	252.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.00	24.00	0.00	12.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1026.00	6134.00	260.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.00	24.00	0.00	12.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1027.00	6134.00	268.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.00	24.00	0.00	12.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1028.00	6134.00	276.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.14	24.00	0.00	13.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1029.00	6134.00	284.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.14	24.00	0.00	13.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1030.00	6134.00	292.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.14	24.00	0.00	13.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1031.00	6134.00	300.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.29	24.00	0.00	14.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1032.00	6134.00	300.67	0.67	0.50	0.00	0.26	3.17	0.08	8.37	26.29	24.00	0.00	14.00	0.61	0.77	31.48	0.00	36.20	60.43	-24.23	-0.28
1033.00	6134.00	308.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.29	24.00	0.00	14.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1034.00	6134.00	316.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.29	24.00	0.00	14.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1035.00	6134.00	324.00	0.00	0.50	50.00	0.26	3.17	0.08	8.37	26.43	24.00	0.00	15.00	0.61	0.77	17.16	8.00	0.00	29.54	0.00	0.00
1037.00	6135.00	0.00	0.00	0.55	50.00	0.23	1.43	0.16	4.23	24.43	24.00	0.00	1.00	-0.09	-0.12	0.00	0.00	0.00	0.00	0.00	0.00
1038.00	6135.00	8.00	0.00	0.60	50.00	0.25	1.54	0.16	4.31	24.57	24.00	0.00	2.00	-0.09	-0.12	9.33	8.00	0.00	8.57	0.00	0.00
1039.00	6135.00	16.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.57	24.00	0.00	2.00	-0.09	-0.12	20.68	8.00	0.00	18.88	0.00	0.00
1040.00	6135.00	24.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.57	24.00	0.00	2.00	-0.09	-0.12	25.59	8.00	0.00	23.44	0.00	0.00
1041.00	6135.00	32.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.71	24.00	0.00	3.00	-0.09	-0.12	27.84	8.00	0.00	25.58	0.00	0.00
1042.00	6135.00	40.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.71	24.00	0.00	3.00	-0.09	-0.12	28.86	8.00	0.00	26.58	0.00	0.00
1043.00	6135.00	48.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.71	24.00	0.00	3.00	-0.09	-0.12	29.33	8.00	0.00	27.05	0.00	0.00
1044.00	6135.00	56.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.86	24.00	0.00	4.00	-0.09	-0.12	29.55	8.00	0.00	27.27	0.00	0.00
1045.00	6135.00	62.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.86	24.00	0.00	4.00	-0.09	-0.12	36.06	6.00	0.00	33.09	0.00	0.00
1046.00	6135.00	70.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	24.86	24.00	0.00	4.00	-0.09	-0.12	32.62	8.00	0.00	30.09	0.00	0.00
1047.00	6135.00	78.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.00	24.00	0.00	5.00	-0.09	-0.12	31.05	8.00	0.00	28.69	0.00	0.00
1048.00	6135.00	86.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.00	24.00	0.00	5.00	-0.09	-0.12	30.33	8.00	0.00	28.04	0.00	0.00
1049.00	6135.00	94.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.00	24.00	0.00	5.00	-0.09	-0.12	30.00	8.00	0.00	27.73	0.00	0.00
1050.00	6135.00	102.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.14	24.00	0.00	6.00	-0.09	-0.12	29.85	8.00	0.00	27.59	0.00	0.00
1051.00	6135.00	110.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.14	24.00	0.00	6.00	-0.09	-0.12	29.78	8.00	0.00	27.52	0.00	0.00
1052.00	6135.00	118.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.14	24.00	0.00	6.00	-0.09	-0.12	29.75	8.00	0.00	27.49	0.00	0.00

1053.00	6135.00	126.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.29	24.00	0.00	7.00	-0.09	-0.12	29.74	8.00	0.00	27.47	0.00	0.00
1054.00	6135.00	134.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.29	24.00	0.00	7.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1055.00	6135.00	142.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.29	24.00	0.00	7.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1056.00	6135.00	150.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.43	24.00	0.00	8.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1057.00	6135.00	158.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.43	24.00	0.00	8.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1058.00	6135.00	166.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.43	24.00	0.00	8.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1059.00	6135.00	174.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.57	24.00	0.00	9.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1060.00	6135.00	182.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.57	24.00	0.00	9.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1061.00	6135.00	190.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.57	24.00	0.00	9.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1062.00	6135.00	198.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.71	24.00	0.00	10.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1063.00	6135.00	206.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.71	24.00	0.00	10.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1064.00	6135.00	214.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.71	24.00	0.00	10.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1065.00	6135.00	222.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.86	24.00	0.00	11.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1066.00	6135.00	225.00	3.00	0.56	0.00	0.14	1.45	0.10	7.08	25.86	24.00	0.00	11.00	-0.09	-0.12	48.50	0.00	55.50	44.14	11.36	0.01
1067.00	6135.00	230.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.86	24.00	0.00	11.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1068.00	6135.00	238.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	25.86	24.00	0.00	11.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1069.00	6135.00	246.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.00	24.00	0.00	12.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1070.00	6135.00	249.83	3.83	0.56	0.00	0.14	1.45	0.10	7.08	26.00	24.00	0.00	12.00	-0.09	-0.12	44.72	0.00	63.60	40.80	22.80	0.31
1071.00	6135.00	254.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.00	24.00	0.00	12.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1072.00	6135.00	262.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.00	24.00	0.00	12.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1073.00	6135.00	270.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.14	24.00	0.00	13.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1074.00	6135.00	278.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.14	24.00	0.00	13.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1075.00	6135.00	286.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.14	24.00	0.00	13.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1076.00	6135.00	294.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.29	24.00	0.00	14.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1077.00	6135.00	302.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.29	24.00	0.00	14.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1078.00	6135.00	310.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.29	24.00	0.00	14.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1079.00	6135.00	318.00	0.00	0.56	50.00	0.14	1.45	0.10	7.08	26.43	24.00	0.00	15.00	-0.09	-0.12	29.73	8.00	0.00	27.46	0.00	0.00
1080.00	6135.00	320.08	2.08	0.56	0.00	0.14	1.45	0.10	7.08	26.43	24.00	0.00	15.00	-0.09	-0.12	53.08	0.00	84.00	48.17	35.83	0.49
1091.00	6143.00	0.00	0.00	0.44	22.00	0.05	0.52	0.10	7.27	23.86	23.00	0.00	1.00	-0.70	-0.90	0.00	0.00	0.00	0.00	0.00	0.00
1092.00	6143.00	8.00	0.00	0.44	22.00	0.04	0.52	0.07	10.08	24.00	23.00	0.00	1.00	-0.70	-0.90	24.66	8.00	0.00	11.05	0.00	0.00

1093.00	6143.00	15.00	7.00	0.44	0.00	0.03	0.52	0.06	11.20	24.00	23.00	0.00	1.00	-0.70	-0.90	43.66	0.00	69.90	19.90	50.00	1.70
1094.00	6143.00	16.00	0.00	0.44	22.00	0.04	0.52	0.08	8.40	24.00	23.00	0.00	1.00	-0.70	-0.90	40.20	8.00	0.00	18.61	0.00	0.00
1095.00	6143.00	24.00	0.00	0.43	22.00	0.04	0.50	0.08	8.88	24.00	23.00	0.00	1.00	-0.70	-0.90	46.14	8.00	0.00	22.42	0.00	0.00
1096.00	6143.00	32.00	0.00	0.43	22.00	0.04	0.50	0.08	8.88	24.14	23.00	0.00	2.00	-0.70	-0.90	48.51	8.00	0.00	24.29	0.00	0.00
1097.00	6143.00	40.00	0.00	0.43	22.00	0.04	0.50	0.07	9.43	24.14	23.00	0.00	2.00	-0.70	-0.90	51.62	8.00	0.00	26.17	0.00	0.00
1098.00	6143.00	48.00	0.00	0.43	22.00	0.04	0.50	0.07	9.43	24.14	23.00	0.00	2.00	-0.70	-0.90	53.34	8.00	0.00	27.34	0.00	0.00
1099.00	6143.00	56.00	0.00	0.43	22.00	0.04	0.50	0.07	9.43	24.29	23.00	0.00	3.00	-0.70	-0.90	54.30	8.00	0.00	28.07	0.00	0.00
1101.00	6153.00	0.00	0.00	1.16	77.00	0.17	1.81	0.09	7.31	31.57	26.00	1.00	33.00	-0.44	-0.62	0.00	0.00	0.00	0.00	0.00	0.00
1102.00	6153.00	8.00	0.00	1.19	77.00	0.22	1.86	0.12	5.88	31.71	26.00	1.00	34.00	-0.44	-0.62	16.61	8.00	0.00	10.37	0.00	0.00
1103.00	6153.00	16.00	0.00	1.21	77.00	0.22	1.89	0.12	5.90	31.71	26.00	1.00	34.00	-0.44	-0.62	22.84	8.00	0.00	14.92	0.00	0.00
1104.00	6153.00	24.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	31.71	26.00	1.00	34.00	-0.44	-0.62	24.67	8.00	0.00	16.57	0.00	0.00
1105.00	6153.00	32.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	31.86	26.00	1.00	35.00	-0.44	-0.62	25.71	8.00	0.00	17.57	0.00	0.00
1106.00	6153.00	40.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	31.86	26.00	1.00	35.00	-0.44	-0.62	26.12	8.00	0.00	18.03	0.00	0.00
1107.00	6153.00	48.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	31.86	26.00	1.00	35.00	-0.44	-0.62	26.28	8.00	0.00	18.24	0.00	0.00
1108.00	6153.00	56.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.00	26.00	1.00	36.00	-0.44	-0.62	26.34	8.00	0.00	18.34	0.00	0.00
1109.00	6153.00	60.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.00	26.00	1.00	36.00	-0.44	-0.62	42.00	4.00	0.00	27.12	0.00	0.00
1110.00	6153.00	68.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.00	26.00	1.00	36.00	-0.44	-0.62	32.54	8.00	0.00	22.42	0.00	0.00
1111.00	6153.00	76.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.14	26.00	1.00	37.00	-0.44	-0.62	28.81	8.00	0.00	20.26	0.00	0.00
1112.00	6153.00	82.50	6.50	1.25	0.00	0.23	1.96	0.12	5.96	32.14	26.00	1.00	37.00	-0.44	-0.62	32.56	0.00	40.60	22.29	18.31	0.22
1113.00	6153.00	84.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.14	26.00	1.00	37.00	-0.44	-0.62	27.34	8.00	0.00	19.26	0.00	0.00
1114.00	6153.00	92.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.14	26.00	1.00	37.00	-0.44	-0.62	26.76	8.00	0.00	18.81	0.00	0.00
1115.00	6153.00	100.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.29	26.00	1.00	38.00	-0.44	-0.62	26.53	8.00	0.00	18.60	0.00	0.00
1116.00	6153.00	108.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.29	26.00	1.00	38.00	-0.44	-0.62	26.44	8.00	0.00	18.50	0.00	0.00
1117.00	6153.00	116.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.29	26.00	1.00	38.00	-0.44	-0.62	26.41	8.00	0.00	18.46	0.00	0.00
1118.00	6153.00	124.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.43	26.00	1.00	39.00	-0.44	-0.62	26.39	8.00	0.00	18.44	0.00	0.00
1119.00	6153.00	130.55	6.55	1.25	0.00	0.23	1.96	0.12	5.96	32.43	26.00	1.00	39.00	-0.44	-0.62	31.24	0.00	38.40	21.22	17.18	0.20
1120.00	6153.00	132.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.43	26.00	1.00	39.00	-0.44	-0.62	26.39	8.00	0.00	18.43	0.00	0.00
1121.00	6153.00	140.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.43	26.00	1.00	39.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1122.00	6153.00	148.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.57	26.00	1.00	40.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1123.00	6153.00	156.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.57	26.00	1.00	40.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00

1124.00	6153.00	164.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.57	26.00	1.00	40.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1125.00	6153.00	172.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.71	26.00	1.00	41.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1126.00	6153.00	180.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.71	26.00	1.00	41.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1127.00	6153.00	188.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.71	26.00	1.00	41.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1128.00	6153.00	196.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.86	26.00	1.00	42.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1129.00	6153.00	204.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.86	26.00	1.00	42.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1130.00	6153.00	212.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	32.86	26.00	1.00	42.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1131.00	6153.00	220.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	33.00	26.00	1.00	43.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1132.00	6153.00	228.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	33.00	26.00	1.00	43.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1133.00	6153.00	230.52	2.52	1.25	0.00	0.23	1.96	0.12	5.96	33.00	26.00	1.00	43.00	-0.44	-0.62	49.92	0.00	84.70	31.38	53.32	1.09
1134.00	6153.00	236.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	33.00	26.00	1.00	43.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1135.00	6153.00	244.00	0.00	1.25	77.00	0.23	1.96	0.12	5.96	33.14	26.00	1.00	44.00	-0.44	-0.62	26.39	8.00	0.00	18.42	0.00	0.00
1136.00	6153.00	247.97	3.97	1.25	0.00	0.23	1.96	0.12	5.96	33.14	26.00	1.00	44.00	-0.44	-0.62	42.17	0.00	60.80	27.26	33.55	0.62
1137.00	6154.00	0.00	0.00	0.85	91.00	0.11	0.87	0.13	5.46	27.57	27.00	1.00	3.00	-0.76	-1.05	0.00	0.00	0.00	0.00	0.00	0.00
1138.00	6154.00	4.42	4.42	0.90	0.00	0.09	0.92	0.10	6.77	27.57	27.00	1.00	3.00	-0.76	-1.05	64.67	0.00	110.00	25.11	84.89	1.89
1139.00	6154.00	9.00	0.00	0.90	91.00	0.09	0.92	0.10	6.77	27.57	27.00	1.00	3.00	-0.76	-1.05	40.47	9.00	0.00	17.67	0.00	0.00
1140.00	6154.00	16.42	7.42	0.90	0.00	0.09	0.92	0.10	6.77	27.71	27.00	1.00	4.00	-0.76	-1.05	66.51	0.00	93.80	29.95	63.85	0.99
1141.00	6154.00	17.00	0.00	0.90	91.00	0.09	0.92	0.10	6.77	27.71	27.00	1.00	4.00	-0.76	-1.05	62.68	8.00	0.00	28.65	0.00	0.00
1142.00	6154.00	24.00	0.00	0.90	91.00	0.09	0.92	0.10	6.77	27.71	27.00	1.00	4.00	-0.76	-1.05	80.28	7.00	0.00	37.35	0.00	0.00
1143.00	6154.00	29.50	5.50	0.90	0.00	0.09	0.92	0.10	6.77	27.71	27.00	1.00	4.00	-0.76	-1.05	103.62	0.00	127.00	47.61	79.39	0.74
1144.00	6160.00	0.00	0.00	0.58	63.00	0.12	2.00	0.06	11.65	24.57	24.00	0.00	4.00	0.04	0.17	0.00	0.00	0.00	0.00	0.00	0.00
1145.00	6160.00	8.00	0.00	0.53	63.00	0.12	1.81	0.07	10.55	24.57	24.00	0.00	4.00	0.04	0.17	20.92	8.00	0.00	23.13	0.00	0.00
1146.00	6160.00	16.00	0.00	0.53	63.00	0.11	1.81	0.06	11.37	24.57	24.00	0.00	4.00	0.04	0.17	34.54	8.00	0.00	37.42	0.00	0.00
1148.00	6160.00	21.83	5.83	0.58	0.00	0.10	2.00	0.05	14.16	24.71	24.00	0.00	5.00	0.04	0.17	47.40	0.00	58.10	51.77	6.33	0.00
1149.00	6160.00	24.00	0.00	0.64	63.00	0.13	2.21	0.06	11.95	24.71	24.00	0.00	5.00	0.04	0.17	37.83	8.00	0.00	40.64	0.00	0.00
1150.00	6160.00	32.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	24.71	24.00	0.00	5.00	0.04	0.17	42.35	8.00	0.00	45.07	0.00	0.00
1151.00	6160.00	36.00	4.00	0.68	0.00	0.12	2.33	0.05	13.84	24.71	24.00	0.00	5.00	0.04	0.17	57.04	0.00	69.20	61.74	7.47	0.01
1152.00	6160.00	40.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	24.71	24.00	0.00	5.00	0.04	0.17	46.69	8.00	0.00	49.22	0.00	0.00
1153.00	6160.00	45.50	5.50	0.68	0.00	0.12	2.33	0.05	13.84	24.86	24.00	0.00	6.00	0.04	0.17	56.21	0.00	27.10	59.74	-32.64	-0.65
1154.00	6160.00	48.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	24.86	24.00	0.00	6.00	0.04	0.17	49.59	8.00	0.00	51.85	0.00	0.00

1155.00	6160.00	56.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	24.86	24.00	0.00	6.00	0.04	0.17	51.54	8.00	0.00	53.53	0.00	0.00
1156.00	6160.00	64.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	24.86	24.00	0.00	6.00	0.04	0.17	52.84	8.00	0.00	54.59	0.00	0.00
1157.00	6160.00	72.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	25.00	24.00	0.00	7.00	0.04	0.17	53.72	8.00	0.00	55.27	0.00	0.00
1158.00	6160.00	77.00	5.00	0.68	0.00	0.12	2.33	0.05	13.84	25.00	24.00	0.00	7.00	0.04	0.17	63.10	0.00	120.00	66.02	53.98	0.71
1159.00	6160.00	80.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	25.00	24.00	0.00	7.00	0.04	0.17	54.30	8.00	0.00	55.70	0.00	0.00
1160.00	6160.00	86.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	25.00	24.00	0.00	7.00	0.04	0.17	60.46	6.00	0.00	62.69	0.00	0.00
1161.00	6160.00	96.00	0.00	0.68	63.00	0.12	2.33	0.05	13.84	25.14	24.00	0.00	8.00	0.04	0.17	53.21	10.00	0.00	53.94	0.00	0.00
1162.00	6160.00	106.25	10.25	0.68	0.00	0.12	2.33	0.05	13.84	25.14	24.00	0.00	8.00	0.04	0.17	48.22	0.00	73.00	48.29	24.71	0.41
1168.00	6166.00	0.00	0.00	0.59	68.50	1.29	12.38	0.10	6.67	24.57	24.00	0.00	2.00	1.72	1.97	0.00	0.00	0.00	0.00	0.00	0.00
1169.00	6166.00	8.00	0.00	0.59	68.50	1.29	12.38	0.10	6.67	24.57	24.00	0.00	2.00	1.72	1.97	2.47	8.00	0.00	14.07	0.00	0.00
1170.00	6166.00	16.00	0.00	0.59	68.50	1.50	12.38	0.12	5.72	24.71	24.00	0.00	3.00	1.72	1.97	3.10	8.00	0.00	15.87	0.00	0.00
1171.00	6166.00	24.00	0.00	0.59	68.50	1.50	12.38	0.12	5.72	24.71	24.00	0.00	3.00	1.72	1.97	3.34	8.00	0.00	16.38	0.00	0.00
1172.00	6166.00	34.00	0.00	0.59	68.50	2.25	12.38	0.18	3.81	24.71	24.00	0.00	3.00	1.72	1.97	1.48	10.00	0.00	5.62	0.00	0.00
1173.00	6166.00	42.00	0.00	0.59	68.50	2.25	12.38	0.18	3.81	24.86	24.00	0.00	4.00	1.72	1.97	1.70	8.00	0.00	7.32	0.00	0.00
1174.00	6166.00	48.00	0.00	0.69	68.50	2.53	14.43	0.18	3.96	24.86	24.00	0.00	4.00	1.72	1.97	2.25	6.00	0.00	10.94	0.00	0.00
1175.00	6166.00	58.00	0.00	0.69	68.50	3.37	14.43	0.23	2.97	24.86	24.00	0.00	4.00	1.72	1.97	0.71	10.00	0.00	2.36	0.00	0.00
1176.00	6166.00	66.00	0.00	0.69	68.50	2.53	14.43	0.18	3.96	25.00	24.00	0.00	5.00	1.72	1.97	1.40	8.00	0.00	6.32	0.00	0.00
1177.00	6166.00	72.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.00	24.00	0.00	5.00	1.72	1.97	2.34	6.00	0.00	11.45	0.00	0.00
1178.00	6166.00	80.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.00	24.00	0.00	5.00	1.72	1.97	1.84	8.00	0.00	7.99	0.00	0.00
1179.00	6166.00	90.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.14	24.00	0.00	6.00	1.72	1.97	1.21	10.00	0.00	4.70	0.00	0.00
1180.00	6166.00	98.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.14	24.00	0.00	6.00	1.72	1.97	1.57	8.00	0.00	6.91	0.00	0.00
1181.00	6166.00	106.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.14	24.00	0.00	6.00	1.72	1.97	1.65	8.00	0.00	7.26	0.00	0.00
1182.00	6166.00	114.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.29	24.00	0.00	7.00	1.72	1.97	1.68	8.00	0.00	7.32	0.00	0.00
1183.00	6166.00	122.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.29	24.00	0.00	7.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1184.00	6166.00	130.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.29	24.00	0.00	7.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1185.00	6166.00	138.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.43	24.00	0.00	8.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1187.00	6166.00	145.92	7.92	0.65	0.00	2.40	13.51	0.18	3.89	25.43	24.00	0.00	8.00	1.72	1.97	1.71	0.00	1.89	7.46	-5.57	-0.22
1188.00	6166.00	146.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.43	24.00	0.00	8.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1189.00	6166.00	150.78	4.78	0.65	0.00	2.40	13.51	0.18	3.89	25.43	24.00	0.00	8.00	1.72	1.97	2.98	0.00	1.94	15.34	-13.40	-0.39
1190.00	6166.00	154.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.43	24.00	0.00	8.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00

1191.00	6166.00	162.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.57	24.00	0.00	9.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1193.00	6166.00	170.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.57	24.00	0.00	9.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1194.00	6166.00	175.22	5.22	0.65	0.00	2.40	13.51	0.18	3.89	25.57	24.00	0.00	9.00	1.72	1.97	2.76	0.00	5.76	13.87	-8.11	-0.08
1195.00	6166.00	178.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.57	24.00	0.00	9.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1197.00	6166.00	186.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.71	24.00	0.00	10.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1198.00	6166.00	188.75	2.75	0.65	0.00	2.40	13.51	0.18	3.89	25.71	24.00	0.00	10.00	1.72	1.97	4.28	0.00	0.15	24.44	-24.29	-0.55
1199.00	6166.00	194.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.71	24.00	0.00	10.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1200.00	6166.00	199.68	5.68	0.65	0.00	2.40	13.51	0.18	3.89	25.71	24.00	0.00	10.00	1.72	1.97	2.54	0.00	0.05	12.48	-12.43	-0.50
1201.00	6166.00	202.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.71	24.00	0.00	10.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1202.00	6166.00	207.92	5.92	0.65	0.00	2.40	13.51	0.18	3.89	25.71	24.00	0.00	10.00	1.72	1.97	2.44	0.00	0.13	11.81	-11.69	-0.49
1203.00	6166.00	210.00	0.00	0.65	68.50	2.40	13.51	0.18	3.89	25.86	24.00	0.00	11.00	1.72	1.97	1.68	8.00	0.00	7.33	0.00	0.00
1205.00	6171.00	0.00	0.00	0.71	38.00	0.42	8.79	0.05	14.37	28.43	24.00	0.00	25.00	1.16	1.45	0.00	0.00	0.00	0.00	0.00	0.00
1206.00	6171.00	8.00	0.00	0.70	38.00	0.54	8.71	0.06	11.27	28.43	24.00	0.00	25.00	1.16	1.45	2.71	8.00	0.00	9.86	0.00	0.00
1207.00	6171.00	16.00	0.00	0.73	38.00	0.55	9.05	0.06	11.38	28.57	24.00	0.00	26.00	1.16	1.45	4.22	8.00	0.00	14.52	0.00	0.00
1209.00	6171.00	23.00	0.00	0.74	38.00	0.41	9.21	0.04	15.58	28.57	24.00	0.00	26.00	1.16	1.45	6.09	7.00	0.00	21.23	0.00	0.00
1210.00	6171.00	31.00	0.00	0.74	38.00	0.41	9.21	0.04	15.58	28.57	24.00	0.00	26.00	1.16	1.45	7.19	8.00	0.00	24.35	0.00	0.00
1211.00	6171.00	39.00	0.00	0.74	38.00	0.41	9.21	0.04	15.58	28.71	24.00	0.00	27.00	1.16	1.45	7.96	8.00	0.00	26.29	0.00	0.00
1213.00	6171.00	48.00	0.00	0.74	38.00	0.41	9.21	0.04	15.58	28.71	24.00	0.00	27.00	1.16	1.45	8.13	9.00	0.00	25.93	0.00	0.00
1214.00	6171.00	54.42	6.42	0.74	0.00	0.41	9.21	0.04	15.58	28.71	24.00	0.00	27.00	1.16	1.45	9.25	0.00	6.79	29.95	-23.16	-0.57
1215.00	6174.00	0.00	0.00	0.77	75.00	0.79	17.28	0.05	15.18	24.57	24.00	0.00	4.00	1.57	2.05	0.00	0.00	0.00	0.00	0.00	0.00
1217.00	6174.00	8.00	0.00	0.77	75.00	0.79	17.28	0.05	15.18	24.71	24.00	0.00	5.00	1.57	2.05	3.05	8.00	0.00	19.04	0.00	0.00
1218.00	6174.00	14.00	0.00	0.68	75.00	0.66	15.21	0.04	15.92	24.71	24.00	0.00	5.00	1.57	2.05	6.51	6.00	0.00	39.77	0.00	0.00
1219.00	6174.00	19.00	5.00	0.68	0.00	0.66	15.21	0.04	15.92	24.71	24.00	0.00	5.00	1.57	2.05	9.25	0.00	1.71	55.45	-53.74	-0.43
1220.00	6174.00	23.00	0.00	0.68	75.00	0.57	15.21	0.04	18.37	24.71	24.00	0.00	5.00	1.57	2.05	7.95	9.00	0.00	43.53	0.00	0.00
1221.00	6174.00	31.00	0.00	0.68	75.00	0.61	15.21	0.04	17.15	24.86	24.00	0.00	6.00	1.57	2.05	9.36	8.00	0.00	49.01	0.00	0.00
1223.00	6174.00	38.00	0.00	0.69	75.00	0.62	15.45	0.04	17.22	24.86	24.00	0.00	6.00	1.57	2.05	10.65	7.00	0.00	54.97	0.00	0.00
1224.00	6174.00	46.00	0.00	0.65	75.00	0.70	14.69	0.05	14.57	24.86	24.00	0.00	6.00	1.57	2.05	11.19	8.00	0.00	53.29	0.00	0.00
1225.00	6174.00	54.00	0.00	0.65	75.00	0.64	14.69	0.04	15.79	25.00	24.00	0.00	7.00	1.57	2.05	11.51	8.00	0.00	53.23	0.00	0.00
1226.00	6174.00	62.00	0.00	0.65	75.00	0.64	14.69	0.04	15.79	25.00	24.00	0.00	7.00	1.57	2.05	11.74	8.00	0.00	53.20	0.00	0.00
1227.00	6174.00	64.00	2.00	0.65	0.00	0.64	14.69	0.04	15.79	25.00	24.00	0.00	7.00	1.57	2.05	15.48	0.00	25.60	81.14	-55.54	-0.24

1228.00	6174.00	70.00	0.00	0.65	75.00	0.64	14.69	0.04	15.79	25.00	24.00	0.00	7.00	1.57	2.05	11.89	8.00	0.00	53.18	0.00	0.00
1229.00	6174.00	78.00	0.00	0.65	75.00	0.64	14.69	0.04	15.79	25.14	24.00	0.00	8.00	1.57	2.05	12.01	8.00	0.00	53.17	0.00	0.00
1230.00	6174.00	80.25	2.25	0.65	0.00	0.64	14.69	0.04	15.79	25.14	24.00	0.00	8.00	1.57	2.05	15.55	0.00	5.88	79.69	-73.81	-0.48
1231.00	6174.00	87.00	0.00	0.65	75.00	0.64	14.69	0.04	15.79	25.14	24.00	0.00	8.00	1.57	2.05	11.56	9.00	0.00	49.55	0.00	0.00
1232.00	6174.00	93.00	6.00	0.65	0.00	0.64	14.69	0.04	15.79	25.14	24.00	0.00	8.00	1.57	2.05	12.85	0.00	4.22	58.83	-54.61	-0.48
1233.00	6174.00	93.00	6.00	0.65	0.00	0.64	14.69	0.04	15.79	25.14	24.00	0.00	8.00	1.57	2.05	12.85	0.00	22.50	58.83	-36.33	-0.16
1234.00	6198.00	0.00	0.00	0.57	28.00	0.16	3.93	0.04	16.74	23.43	23.00	0.00	3.00	0.68	0.87	0.00	0.00	0.00	0.00	0.00	0.00
1235.00	6198.00	31.00	0.00	0.57	28.00	0.19	3.93	0.05	14.10	23.57	23.00	0.00	4.00	0.68	0.87	1.57	31.00	0.00	2.75	0.00	0.00
1236.00	6198.00	39.00	0.00	0.59	28.00	0.20	4.08	0.05	14.23	23.57	23.00	0.00	4.00	0.68	0.87	5.73	8.00	0.00	12.06	0.00	0.00
1237.00	6198.00	47.00	0.00	0.59	28.00	0.19	4.08	0.05	15.12	23.71	23.00	0.00	5.00	0.68	0.87	8.78	8.00	0.00	18.44	0.00	0.00
1239.00	6198.00	56.00	0.00	0.59	28.00	0.18	4.08	0.04	16.01	23.71	23.00	0.00	5.00	0.68	0.87	10.65	9.00	0.00	21.92	0.00	0.00
1240.00	6198.00	60.58	4.58	0.59	0.00	0.18	4.08	0.04	16.01	23.71	23.00	0.00	5.00	0.68	0.87	14.43	0.00	2.70	30.34	-27.65	-0.60
1241.00	6198.00	64.00	0.00	0.59	28.00	0.18	4.08	0.04	16.01	23.71	23.00	0.00	5.00	0.68	0.87	12.44	8.00	0.00	25.38	0.00	0.00
1242.00	6198.00	69.05	5.05	0.59	0.00	0.18	4.08	0.04	16.01	23.86	23.00	0.00	6.00	0.68	0.87	15.57	0.00	17.00	32.27	-15.27	-0.19
1243.00	6198.00	72.33	8.33	0.59	0.00	0.18	4.08	0.04	16.01	23.86	23.00	0.00	6.00	0.68	0.87	13.51	0.00	4.63	27.19	-22.56	-0.54
1244.00	6198.00	74.00	0.00	0.59	28.00	0.18	4.08	0.04	16.01	23.86	23.00	0.00	6.00	0.68	0.87	12.57	10.00	0.00	24.92	0.00	0.00
1245.00	6198.00	78.92	4.92	0.59	0.00	0.18	4.08	0.04	16.01	23.86	23.00	0.00	6.00	0.68	0.87	15.77	0.00	33.20	32.13	1.07	0.31
1246.00	6198.00	85.25	11.25	0.59	0.00	0.18	4.08	0.04	16.01	23.86	23.00	0.00	6.00	0.68	0.87	11.99	0.00	14.50	23.08	-8.58	-0.09
1247.00	6200.00	0.00	0.00	1.09	125.00	0.49	5.47	0.09	7.75	31.43	29.00	1.00	12.00	0.43	0.55	0.00	0.00	0.00	0.00	0.00	0.00
1248.00	6200.00	8.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.43	29.00	1.00	12.00	0.43	0.55	10.27	8.00	0.00	16.66	0.00	0.00
1249.00	6200.00	16.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.57	29.00	1.00	13.00	0.43	0.55	16.30	8.00	0.00	25.80	0.00	0.00
1250.00	6200.00	24.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.57	29.00	1.00	13.00	0.43	0.55	19.83	8.00	0.00	30.81	0.00	0.00
1251.00	6200.00	32.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.57	29.00	1.00	13.00	0.43	0.55	21.90	8.00	0.00	33.56	0.00	0.00
1252.00	6200.00	40.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.71	29.00	1.00	14.00	0.43	0.55	23.12	8.00	0.00	35.06	0.00	0.00
1253.00	6200.00	41.83	1.83	1.44	0.00	0.48	7.26	0.07	10.39	31.71	29.00	1.00	14.00	0.43	0.55	35.96	0.00	44.20	57.04	-12.84	-0.16
1254.00	6200.00	49.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.71	29.00	1.00	14.00	0.43	0.55	22.29	9.00	0.00	33.29	0.00	0.00
1255.00	6200.00	57.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.71	29.00	1.00	14.00	0.43	0.55	23.35	8.00	0.00	34.92	0.00	0.00
1256.00	6200.00	65.00	0.00	1.44	125.00	0.48	7.26	0.07	10.39	31.86	29.00	1.00	15.00	0.43	0.55	23.96	8.00	0.00	35.81	0.00	0.00
1258.00	6211.00	0.00	0.00	0.69	55.00	0.05	0.83	0.06	11.96	27.00	25.00	0.00	13.00	-0.80	-0.89	0.00	0.00	0.00	0.00	0.00	0.00
1259.00	6211.00	6.00	0.00	0.69	55.00	0.05	0.83	0.06	11.96	27.00	25.00	0.00	13.00	-0.80	-0.89	47.54	6.00	0.00	20.07	0.00	0.00

1260.00	6211.00	12.00	0.00	0.69	55.00	0.05	0.82	0.06	11.92	27.14	25.00	0.00	14.00	-0.80	-0.89	81.98	6.00	0.00	35.04	0.00	0.00
1261.00	6211.00	17.00	0.00	0.69	55.00	0.05	0.82	0.06	11.92	27.14	25.00	0.00	14.00	-0.80	-0.89	112.23	5.00	0.00	48.25	0.00	0.00
1262.00	6211.00	22.00	0.00	0.65	55.00	0.10	0.78	0.13	5.54	27.14	25.00	0.00	14.00	-0.80	-0.89	101.89	5.00	0.00	45.35	0.00	0.00
1263.00	6211.00	28.00	0.00	0.65	55.00	0.10	0.78	0.13	5.54	27.14	25.00	0.00	14.00	-0.80	-0.89	82.43	6.00	0.00	37.81	0.00	0.00
1264.00	6211.00	34.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.29	25.00	0.00	15.00	-0.80	-0.89	110.21	6.00	0.00	49.44	0.00	0.00
1265.00	6211.00	40.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.29	25.00	0.00	15.00	-0.80	-0.89	130.12	6.00	0.00	58.01	0.00	0.00
1266.00	6211.00	46.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.29	25.00	0.00	15.00	-0.80	-0.89	144.38	6.00	0.00	64.33	0.00	0.00
1267.00	6211.00	52.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.29	25.00	0.00	15.00	-0.80	-0.89	154.59	6.00	0.00	68.99	0.00	0.00
1268.00	6211.00	58.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.43	25.00	0.00	16.00	-0.80	-0.89	161.92	6.00	0.00	72.42	0.00	0.00
1269.00	6211.00	60.25	2.25	0.65	0.00	0.04	0.78	0.06	12.47	27.43	25.00	0.00	16.00	-0.80	-0.89	205.89	0.00	94.10	90.69	3.41	-0.69
1270.00	6211.00	64.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.43	25.00	0.00	16.00	-0.80	-0.89	167.16	6.00	0.00	74.95	0.00	0.00
1271.00	6211.00	70.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.43	25.00	0.00	16.00	-0.80	-0.89	170.92	6.00	0.00	76.82	0.00	0.00
1272.00	6211.00	76.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.43	25.00	0.00	16.00	-0.80	-0.89	173.61	6.00	0.00	78.20	0.00	0.00
1274.00	6211.00	82.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.57	25.00	0.00	17.00	-0.80	-0.89	175.54	6.00	0.00	79.21	0.00	0.00
1276.00	6211.00	88.00	0.00	0.65	55.00	0.04	0.78	0.06	12.47	27.57	25.00	0.00	17.00	-0.80	-0.89	176.92	6.00	0.00	79.96	0.00	0.00
1277.00	6211.00	94.00	6.00	0.65	0.00	0.04	0.78	0.06	12.47	27.57	25.00	0.00	17.00	-0.80	-0.89	177.91	0.00	432.00	80.51	351.49	3.65
1278.00	6211.00	140.00	0.00	0.65	36.00	0.04	0.78	0.06	12.47	27.86	25.00	0.00	19.00	-0.80	-0.89	13.81	52.00	0.00	7.78	0.00	0.00
1279.00	6211.00	144.33	4.33	0.65	0.00	0.04	0.78	0.06	12.47	27.86	25.00	0.00	19.00	-0.80	-0.89	47.59	0.00	32.40	21.60	10.80	-0.45
1280.00	6211.00	146.00	0.00	0.65	36.00	0.04	0.78	0.06	12.47	27.86	25.00	0.00	19.00	-0.80	-0.89	43.37	6.00	0.00	19.85	0.00	0.00
1281.00	6211.00	157.42	11.42	0.65	0.00	0.04	0.78	0.06	12.47	28.00	25.00	0.00	20.00	-0.80	-0.89	47.77	0.00	29.40	21.83	7.57	-0.60
1282.00	6231.00	0.00	0.00	1.26	95.00	0.68	8.58	0.08	8.76	31.14	29.00	1.00	15.00	0.76	0.85	0.00	0.00	0.00	0.00	0.00	0.00
1283.00	6231.00	6.00	0.00	1.26	95.00	0.68	8.58	0.08	8.76	31.14	29.00	1.00	15.00	0.76	0.85	7.02	6.00	0.00	15.77	0.00	0.00
1284.00	6231.00	12.00	0.00	1.32	95.00	1.06	8.99	0.12	5.91	31.29	29.00	1.00	16.00	0.76	0.85	8.70	6.00	0.00	18.84	0.00	0.00
1285.00	6231.00	18.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.29	29.00	1.00	16.00	0.76	0.85	10.27	6.00	0.00	21.81	0.00	0.00
1286.00	6231.00	24.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.29	29.00	1.00	16.00	0.76	0.85	10.72	6.00	0.00	22.54	0.00	0.00
1287.00	6231.00	30.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.29	29.00	1.00	16.00	0.76	0.85	10.94	6.00	0.00	22.87	0.00	0.00
1288.00	6231.00	37.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.43	29.00	1.00	17.00	0.76	0.85	9.81	7.00	0.00	20.21	0.00	0.00
1289.00	6231.00	42.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.43	29.00	1.00	17.00	0.76	0.85	11.83	5.00	0.00	24.84	0.00	0.00
1290.00	6231.00	44.75	2.75	1.23	0.00	1.00	8.38	0.12	5.80	31.43	29.00	1.00	17.00	0.76	0.85	16.93	0.00	25.40	36.52	-11.12	-0.14
1291.00	6231.00	48.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.43	29.00	1.00	17.00	0.76	0.85	11.49	6.00	0.00	23.92	0.00	0.00



1292.00	6231.00	54.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.43	29.00	1.00	17.00	0.76	0.85	11.32	6.00	0.00	23.51	0.00	0.00
1293.00	6231.00	60.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.57	29.00	1.00	18.00	0.76	0.85	11.24	6.00	0.00	23.31	0.00	0.00
1294.00	6231.00	65.17	5.17	1.23	0.00	1.00	8.38	0.12	5.80	31.57	29.00	1.00	18.00	0.76	0.85	12.36	0.00	10.75	25.88	-15.13	-0.41
1295.00	6231.00	66.00	0.00	1.23	95.00	1.00	8.38	0.12	5.80	31.57	29.00	1.00	18.00	0.76	0.85	11.20	6.00	0.00	23.23	0.00	0.00
1296.00	6231.00	75.08	9.08	1.23	0.00	1.00	8.38	0.12	5.80	31.57	29.00	1.00	18.00	0.76	0.85	7.74	0.00	10.30	15.53	-5.23	-0.15
1297.00	6249.00	0.00	0.00	2.28	100.00	1.66	5.00	0.33	2.09	38.14	27.00	1.00	75.00	-0.29	-0.28	0.00	0.00	0.00	0.00	0.00	0.00
1298.00	6249.00	8.00	0.00	2.28	100.00	1.66	5.00	0.33	2.09	38.29	27.00	1.00	76.00	-0.29	-0.28	1.53	8.00	0.00	1.13	0.00	0.00
1299.00	6249.00	13.67	5.67	2.28	0.00	1.66	5.00	0.33	2.09	38.29	27.00	1.00	76.00	-0.29	-0.28	3.54	0.00	5.38	2.63	2.75	0.83
1300.00	6249.00	17.00	0.00	2.28	100.00	1.66	5.00	0.33	2.09	38.29	27.00	1.00	76.00	-0.29	-0.28	1.17	9.00	0.00	0.86	0.00	0.00
1302.00	6260.00	0.00	0.00	0.54	55.00	0.02	0.32	0.07	10.29	25.43	23.00	0.00	14.00	-1.35	-1.58	0.00	0.00	0.00	0.00	0.00	0.00
1304.00	6260.00	4.75	4.75	0.55	0.00	0.02	0.33	0.06	10.91	25.43	23.00	0.00	14.00	-1.35	-1.58	126.33	0.00	124.00	27.63	96.37	0.38
1305.00	6260.00	8.00	0.00	0.55	55.00	0.02	0.33	0.06	10.91	25.43	23.00	0.00	14.00	-1.35	-1.58	102.77	8.00	0.00	23.45	0.00	0.00
1306.00	6260.00	16.00	0.00	0.55	55.00	0.02	0.33	0.06	10.91	25.57	23.00	0.00	15.00	-1.35	-1.58	164.60	8.00	0.00	39.13	0.00	0.00
1308.00	6260.00	24.67	8.67	0.55	0.00	0.02	0.33	0.06	10.91	25.57	23.00	0.00	15.00	-1.35	-1.58	193.38	0.00	378.00	47.95	330.05	4.37
1309.00	6260.00	24.75	8.75	0.55	0.00	0.02	0.33	0.06	10.91	25.57	23.00	0.00	15.00	-1.35	-1.58	192.40	0.00	285.00	47.76	237.24	2.52
1325.00	11117.00	0.00	0.00	0.88	75.00	0.63	2.28	0.28	2.51	32.86	28.00	1.00	33.00	-0.14	-0.12	0.00	0.00	0.00	0.00	0.00	0.00
1326.00	11117.00	7.60	0.00	0.85	75.00	0.61	2.19	0.28	2.49	32.86	28.00	1.00	33.00	-0.14	-0.12	4.41	7.60	0.00	3.73	0.00	0.00
1327.00	11117.00	15.55	0.00	0.86	75.00	0.62	2.23	0.28	2.50	33.00	28.00	1.00	34.00	-0.14	-0.12	4.44	7.95	0.00	3.73	0.00	0.00
1328.00	11117.00	23.93	0.00	0.86	75.00	0.62	2.23	0.28	2.50	33.00	28.00	1.00	34.00	-0.14	-0.12	3.95	8.38	0.00	3.30	0.00	0.00
1329.00	11117.00	31.77	0.00	0.88	75.00	0.63	2.27	0.28	2.51	33.00	28.00	1.00	34.00	-0.14	-0.12	4.50	7.83	0.00	3.78	0.00	0.00
1330.00	11117.00	39.27	7.50	0.87	0.00	0.62	2.25	0.28	2.50	33.14	28.00	1.00	35.00	-0.14	-0.12	5.05	0.00	7.16	4.25	2.91	0.63
1331.00	11117.00	39.27	7.50	0.87	0.00	0.62	2.25	0.28	2.50	33.14	28.00	1.00	35.00	-0.14	-0.12	5.05	0.00	0.15	4.25	-4.10	-1.08
1332.00	11117.00	39.73	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.14	28.00	1.00	35.00	-0.14	-0.12	4.45	7.97	0.00	3.73	0.00	0.00
1333.00	11117.00	48.25	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.14	28.00	1.00	35.00	-0.14	-0.12	3.80	8.52	0.00	3.17	0.00	0.00
1334.00	11117.00	55.60	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.14	28.00	1.00	35.00	-0.14	-0.12	5.17	7.35	0.00	4.35	0.00	0.00
1335.00	11117.00	62.68	7.08	0.86	0.00	0.62	2.24	0.28	2.50	33.29	28.00	1.00	36.00	-0.14	-0.12	5.76	0.00	11.30	4.86	6.44	1.30
1336.00	11117.00	63.53	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.29	28.00	1.00	36.00	-0.14	-0.12	4.55	7.93	0.00	3.82	0.00	0.00
1337.00	11117.00	71.78	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.29	28.00	1.00	36.00	-0.14	-0.12	4.10	8.25	0.00	3.43	0.00	0.00
1338.00	11117.00	80.12	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.29	28.00	1.00	36.00	-0.14	-0.12	3.96	8.33	0.00	3.31	0.00	0.00
1339.00	11117.00	86.20	6.08	0.86	0.00	0.62	2.24	0.28	2.50	33.43	28.00	1.00	37.00	-0.14	-0.12	7.38	0.00	9.79	6.27	3.52	0.51

1340.00	11117.00	87.82	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.43	28.00	1.00	37.00	-0.14	-0.12	4.71	7.70	0.00	3.96	0.00	0.00
1341.00	11117.00	96.25	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.43	28.00	1.00	37.00	-0.14	-0.12	3.92	8.43	0.00	3.27	0.00	0.00
1342.00	11117.00	103.70	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.43	28.00	1.00	37.00	-0.14	-0.12	5.04	7.45	0.00	4.24	0.00	0.00
1343.00	11117.00	111.72	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.57	28.00	1.00	38.00	-0.14	-0.12	4.43	8.02	0.00	3.71	0.00	0.00
1344.00	11117.00	119.88	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.57	28.00	1.00	38.00	-0.14	-0.12	4.19	8.17	0.00	3.51	0.00	0.00
1345.00	11117.00	127.82	0.00	0.86	75.00	0.62	2.24	0.28	2.50	33.57	28.00	1.00	38.00	-0.14	-0.12	4.43	7.93	0.00	3.72	0.00	0.00
1346.00	11117.00	134.68	6.86	0.86	0.00	0.62	2.24	0.28	2.50	33.71	28.00	1.00	39.00	-0.14	-0.12	6.02	0.00	0.15	5.08	-4.93	-1.09
1373.00	11143.00	0.00	0.00	2.58	185.00	0.43	1.05	0.41	1.70	36.86	29.00	1.00	50.00	-1.18	-1.97	0.00	0.00	0.00	0.00	0.00	0.00
1374.00	11143.00	7.75	0.00	2.58	185.00	0.43	1.05	0.41	1.70	36.86	29.00	1.00	50.00	-1.18	-1.97	8.29	7.75	0.00	6.17	0.00	0.00
1375.00	11143.00	16.02	0.00	2.58	185.00	0.43	1.05	0.41	1.68	37.00	29.00	1.00	51.00	-1.18	-1.97	6.70	8.27	0.00	6.82	0.00	0.00
1376.00	11143.00	23.98	0.00	2.58	185.00	0.43	1.05	0.41	1.68	37.00	29.00	1.00	51.00	-1.18	-1.97	7.56	7.97	0.00	7.38	0.00	0.00
1377.00	11143.00	31.63	0.00	2.58	185.00	0.43	1.05	0.41	1.68	37.00	29.00	1.00	51.00	-1.18	-1.97	8.63	7.65	0.00	7.95	0.00	0.00
1378.00	11143.00	39.17	0.00	2.58	185.00	0.44	1.05	0.42	1.66	37.14	29.00	1.00	52.00	-1.18	-1.97	8.74	7.53	0.00	8.11	0.00	0.00
1379.00	11143.00	49.58	0.00	2.58	185.00	0.44	1.05	0.42	1.66	37.14	29.00	1.00	52.00	-1.18	-1.97	2.63	10.42	0.00	4.74	0.00	0.00
1380.00	11143.00	56.50	0.00	2.58	185.00	0.44	1.05	0.42	1.66	37.14	29.00	1.00	52.00	-1.18	-1.97	11.00	6.92	0.00	8.25	0.00	0.00
1381.00	11143.00	64.20	0.00	2.58	185.00	0.44	1.05	0.42	1.64	37.29	29.00	1.00	53.00	-1.18	-1.97	7.95	7.70	0.00	7.80	0.00	0.00
1382.00	11143.00	72.35	0.00	2.58	185.00	0.44	1.05	0.42	1.64	37.29	29.00	1.00	53.00	-1.18	-1.97	6.47	8.15	0.00	7.06	0.00	0.00
1383.00	11143.00	79.58	0.00	2.58	185.00	0.44	1.05	0.42	1.64	37.29	29.00	1.00	53.00	-1.18	-1.97	9.49	7.23	0.00	8.24	0.00	0.00
1384.00	11143.00	87.87	0.00	2.58	185.00	0.45	1.05	0.43	1.62	37.43	29.00	1.00	54.00	-1.18	-1.97	5.89	8.28	0.00	6.83	0.00	0.00
1385.00	11143.00	95.57	7.70	2.58	0.00	0.45	1.05	0.43	1.62	37.43	29.00	1.00	54.00	-1.18	-1.97	7.46	0.00	7.79	7.34	0.45	-1.72
1386.00	11143.00	95.65	0.00	2.58	185.00	0.45	1.05	0.43	1.62	37.43	29.00	1.00	54.00	-1.18	-1.97	7.20	7.78	0.00	7.23	0.00	0.00
1387.00	11143.00	96.73	1.08	2.58	0.00	0.45	1.05	0.43	1.62	37.43	29.00	1.00	54.00	-1.18	-1.97	141.53	0.00	254.00	27.79	226.21	5.64
1388.00	11143.00	103.40	0.00	2.58	185.00	0.45	1.05	0.43	1.62	37.43	29.00	1.00	54.00	-1.18	-1.97	8.10	7.75	0.00	7.62	0.00	0.00

## References

1. Suyagh M, Collier PS, Millership JS, et al. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. *Pediatrics*. 2011;127(2):e367–374.
2. Wade KC, Wu D, Kaufman DA, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother*. 2008;52(11):4043–4049.
3. Houghton GW, Smith J, Thorne PS, Templeton R. The pharmacokinetics of oral and intravenous metronidazole in man. *J Antimicrob Chemother*. 1979;5(5):621–623.
4. Jensen JC, Gugler R. Single- and multiple-dose metronidazole kinetics. *Clin Pharmacol Ther*. 1983;34(4):481–487.
5. Kacet N, Roussel-Delvallez M, Gremillet C, Dubos JP, Storme L, Lequien P. Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. *Pediatr Infect Dis J*. 1992;11(5):365–369.
6. Reed MD, Goldfarb J, Yamashita TS, Lemon E, Blumer JL. Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother*. 1994;38(12):2817–2826.
7. Upadhyaya P, Bhatnagar V, Basu N. Pharmacokinetics of intravenous metronidazole in neonates. *J Pediatr Surg*. 1988;23(3):263–265.
8. Arzuaga A, Isla A, Gascón AR, et al. Quantitation and stability of piperacillin and tazobactam in plasma and ultrafiltrate from patients undergoing continuous venovenous hemofiltration by HPLC. *Biomed Chromatogr*. 2005;19(8):570–578.
9. Menelaou A, Somogyi AA, Barclay ML, Bochner F. Simultaneous quantification of amoxicillin and metronidazole in plasma using high-performance liquid chromatography with photodiode array detection. *J Chromatogr B Biomed Sci Appl*. 1999;731(2):261–266.