MODULE 2.7 CLINICAL SUMMARY

2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

Generic name: TMC278

Status: Approved **Issued Date:** [redacted]-[redacted]-20[redacted]

TABLE OF CONTENTS

Table of Contents 2
List of In-Text Tables 8
List of In-Text Figures 14
List of Abbreviations 17
1 Background and Overview 21
1.1 Human Biomaterial Studies 23
1.2 Clinical Pharmacology Trials 25
1.3 Bioanalytical Methods 29
1.4 Absorption 29
1.5 Distribution 30
1.6 Metabolism and Excretion 30
1.7 Pharmacokinetics of TMC278 After Single- and Multiple-Dose Administration in Healthy Subjects 30
1.8 Pharmacokinetics of TMC278 After Single- and Multiple-Dose Administration in HIV-1 Infected Subjects 31
1.9 Comparison of Exposure to TMC278 Between Healthy Subjects and HIV-1 Infected Subjects 31
1.10 Effect of Intrinsic Factors 32
1.11 Effect of Extrinsic Factors 32
1.11.1 Impact of Concomitant Food Intake 32
1.11.2 Drug-Drug Interactions 32
1.12 Pharmacodynamics - Efficacy 33
1.13 Pharmacokinetic/Pharmacodynamic Relationships for Efficacy Parameters 33
1.14 Pharmacokinetic/Pharmacodynamic Relationships for Safety Parameters 33
1.14.1 Relationships Between Pharmacokinetics and Adverse Events 33
1.14.2 Relationships Between Pharmacokinetics and Laboratory Parameters 33
1.14.3 Effect of TMC278 on QTcF Interval 33
2 Summary of Results of Individual Trials 35
2.1 Human Biomaterial Studies 35
2.1.1 In Vitro Transport Characteristics: Study NC104 35
2.1.2 Protein Binding: Study NC112 35
2.1.3 In Vitro and in Vivo Metabolism and Potential for Interactions 36
2.1.3.1 Study NC102: In Vitro Metabolism of ^{14}C-TMC278 in Hepatocytes and Liver Subcellular Fractions 36
2.1.3.2 Study NC157 (C119): In Vivo Metabolism of ^{14}C-TMC278 in Human Urine, Feces, and Plasma 38
2.1.3.3 Study NC141: Characterization of Cytochrome P450 Enzymes Involved in Metabolism of TMC278 and Determination of Kinetics of TMC278 Metabolism in Liver Microsomes 40
2.1.3.4 Study FK4123: Interactions Between TMC278 and CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, and CYP4A Activities in Human Liver Microsomes 41

2.1.3.5 Study NC186: In Vitro Potential of TMC278 to Induce CYP Enzyme Activities in Cryopreserved Human Hepatocytes....41
2.1.3.6 Study NC283: In Vitro Potential of TMC278 to Inhibit Paclitaxel and S-Warfarin Metabolism....43
2.1.3.7 Study NC194: In Vitro Potential of TMC278 to Inhibit the Metabolism of Sertraline, Paroxetine, Clarithromycin, Sildenafil, Omeprazole, Chlorzoxazone, 17α-Ethinylestradiol, S-Mephenytoin, and Norethindrone....43
2.2 Mass-Balance of TMC278 in Healthy Subjects: Trial C119....44
2.2.1 Trial Design....44
2.2.2 Pharmacokinetics of TMC278 and Total ^{14}C-Radioactivity....44
2.2.3 Blood Concentration-Time Profiles of Total ^{14}C-Radioactivity....45
2.2.4 Mass-Balance of TMC278, and Metabolite Profiling and Identification....45
2.2.5 Conclusions....46
2.3 Single-Dose Pharmacokinetics of TMC278 in Healthy Subjects....46
2.3.1 Trial CDE-101: Single-Dose Escalation of TMC278 Administered as Oral Solution at Doses of 12.5 to 50 mg in Healthy Subjects....47
2.3.1.1 Trial Design....47
2.3.1.2 Pharmacokinetics of TMC278....47
2.3.1.3 Ex Vivo Antiviral Activity....48
2.3.1.4 Conclusions....48
2.3.2 Trial CDE-103: Single-Dose Escalation of TMC278 Administered as Oral Solution at Doses of 50 to 300 mg in Healthy Subjects....49
2.3.2.1 Trial Design....49
2.3.2.2 Pharmacokinetics of TMC278....49
2.3.2.3 Ex Vivo Antiviral Activity....50
2.3.2.4 Conclusions....50
2.4 Multiple-Dose Pharmacokinetics of TMC278 in Healthy Subjects....51
2.4.1 Trial CDE-102: Multiple-Dose Escalation of TMC278 Administered as Oral Solution at Doses of 25 to 150 mg q.d. in Healthy Subjects....51
2.4.1.1 Trial Design....51
2.4.1.2 Pharmacokinetics of TMC278....51
2.4.1.3 Ex Vivo Antiviral Activity....53
2.4.1.4 Conclusions....54
2.4.2 Trial C103: Multiple-Dose Ranging Trial of TMC278 Administered as Oral Tablet at Doses of 25 to 150 mg in Healthy Subjects....55
2.4.2.1 Trial Design....55
2.4.2.2 Pharmacokinetics of TMC278....55
2.4.2.3 Conclusions....56
2.5 Single-Dose Pharmacokinetics of TMC278 in HIV-1 Infected Subjects....56
2.6 Multiple-Dose Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Relationships of TMC278 in HIV-1 Infected Subjects....57
2.6.1 Phase IIa (Proof-of-Principle) Trials....57
2.6.1.1 Trial C201: Efficacy of TMC278 Monotherapy in Treatment-Naïve, HIV-1 Infected Subjects....57

2.6.1.2 Trial C202: Efficacy of TMC278 Functional Monotherapy in Treatment-Experienced, HIV-1 Infected Subjects....60
2.6.2 Phase IIb Dose-Finding Trial: Trial C204....63
2.6.2.1 Trial Design....63
2.6.2.2 Pharmacokinetics of TMC278 (Substudy)....64
2.6.2.3 Pharmacokinetics of Zidovudine and Zidovudine-Glucuronide (Substudy)....65
2.6.2.4 Pharmacokinetics of TMC278 (Main Trial)....66
2.6.2.5 Pharmacodynamics....67
2.6.2.6 Pharmacokinetic/Pharmacodynamic Relationships for Efficacy Parameters....68
2.6.2.7 Pharmacokinetic/Pharmacodynamic Relationships for Safety Parameters....69
2.6.2.8 Conclusions....69
2.6.3 Phase III Trials....70
2.6.3.1 Trial C209: Long-Term Efficacy, Safety, and Tolerability of TMC278 in Combination with Tenofovir Disoproxil Fumarate and Emtricitabine in Treatment-Naïve HIV-1 Infected Subjects....70
2.6.3.2 Trial C215: Long-Term Efficacy, Safety, and Tolerability of TMC278 in Combination with 2 N(t)RTIs in Treatment-Naïve HIV-1 Infected Subjects....74
2.7 Effect of Intrinsic Factors: Trial C130 on Effect of Hepatic Impairment....78
2.7.1 Trial Design....78
2.7.2 Pharmacokinetics of TMC278 in Subjects With Mild Hepatic Impairment....78
2.7.3 Pharmacokinetics of TMC278 in Subjects With Moderate Hepatic Impairment....79
2.7.4 Conclusions....80
2.8 Effect of Extrinsic Factors: Concomitant Administration of TMC278 With Other Drugs....80
2.8.1 Administration of TMC278 With Other Antiretrovirals (Healthy Subjects)....80
2.8.1.1 Trial C104: Tenofovir Disoproxil Fumarate....80
2.8.1.2 Trial C106: Didanosine....82
2.8.1.3 Trial C105: Lopinavir With Low-Dose Ritonavir....84
2.8.1.4 Trial C112: Darunavir With Low-Dose Ritonavir....86
2.8.2 Administration of TMC278 with Other Antiretrovirals (HIV-1 Infected Subjects)....89
2.8.2.1 Trial C101: Efavirenz and Nevirapine....89
2.8.3 Administration of TMC278 with Drugs Other than Antiretrovirals (Healthy Subjects)....91
2.8.3.1 Trial C108: Rifampin....91
2.8.3.2 Trial C125: Rifabutin....93
2.8.3.3 Trial C127: Ketoconazole....95
2.8.3.4 Trial C123: Sildenafil....97
2.8.3.5 Trial C116: Atorvastatin....99
2.8.3.6 Trial C120: Ethinylestradiol With Norethindrone (Oral Contraceptive) Coadministered With TMC278 150 mg q.d....103

2.8.3.7 Trial C136: Ethinylestradiol With Norethindrone (Oral Contraceptive) Coadministered With TMC278 25 mg q.d. 106
2.8.3.8 Trial C121: Methadone 108
2.8.3.9 Trial C114: Omeprazole 111
2.8.3.10 Trial C140: Famotidine 116
2.8.3.11 Trial C109: Paracetamol (Acetaminophen) 118
2.8.3.12 Trial C139: Chlorzoxazone 121
2.9 Effect of TMC278 on QTcF Interval in Healthy Subjects 123
2.9.1 Trial C131: Thorough QT/QTc Trial on the Effect of TMC278 (75 and 300 mg q.d.) on ECG Intervals 123
2.9.1.1 Trial Design 123
2.9.1.2 Pharmacokinetics of TMC278 124
2.9.1.3 Pharmacokinetics of Moxifloxacin 126
2.9.1.4 Pharmacokinetic/Pharmacodynamic Relationship for TMC278 126
2.9.1.5 Effect of TMC278 on CYP3A4 Activity 129
2.9.1.6 Conclusions 129
2.9.2 Trial C151: Pilot QT/QTc Trial on the Effect of TMC278 (25 mg q.d.) on ECG Intervals 130
2.9.2.1 Trial Design 130
2.9.2.2 Pharmacokinetics of TMC278 130
2.9.2.3 Pharmacokinetics of Moxifloxacin 132
2.9.2.4 Pharmacokinetic/Pharmacodynamic Relationship for TMC278 132
2.9.2.5 Conclusions 134
2.9.3 Trial C152: Thorough QT/QTc Trial on the Effect of TMC278 (25 mg q.d.) and Efavirenz on ECG Intervals 134
2.9.3.1 Trial Design 134
2.9.3.2 Pharmacokinetics of TMC278 135
2.9.3.3 Pharmacokinetics of Moxifloxacin 137
2.9.3.4 Pharmacokinetics of Efavirenz 137
2.9.3.5 Pharmacokinetic/Pharmacodynamic Relationships for TMC278 and Efavirenz 138
2.9.3.6 Conclusions 141
3 Comparison and Analyses of Results Across Trials 142
3.1 Absorption 142
3.1.1 In Vitro Absorption Studies 142
3.1.2 Clinical Trials Evaluating Factors Affecting TMC278 Absorption 142
3.1.2.1 Effect of Concomitant Food Intake 142
3.1.2.2 Effect of Increased Intragastric pH 143
3.2 Distribution 144
3.3 Metabolism and Excretion 144
3.3.1 In Vitro and In Vivo Metabolism and Interaction Potential 144
3.3.1.1 Pathways 144
3.3.1.2 Antiviral Activity of Metabolites 145
3.3.1.3 Key Cytochrome P450 Form/Interaction Potential 145
3.3.2 Clinical Trials: Mass-Balance 146

3.4 Pharmacokinetics of TMC278 After Single- and Multiple-Dose Administration in Healthy Subjects 147
3.4.1 Single-Dose Pharmacokinetics of TMC278 in Healthy Subjects 147
3.4.1.1 TMC278 Administered as Oral Solution 147
3.4.1.2 TMC278 Administered as Phase IIb Tablet 148
3.4.1.3 TMC278 Administered as Phase III Tablet 148
3.4.2 Multiple-Dose Pharmacokinetics of TMC278 in Healthy Subjects 149
3.4.2.1 TMC278 Administered as Oral Solution 149
3.4.2.2 TMC278 Administered as Phase IIb Tablet 150
3.4.2.3 TMC278 Administered as Phase III Tablet 151
3.4.3 Conclusions on Pharmacokinetics of TMC278 in Healthy Subjects 152
3.5 Pharmacokinetics of TMC278 In HIV-1 Infected Subjects 152
3.5.1 Pharmacokinetic Parameters Derived from Intensive Sampling After Single- and Multiple-Dose Administration to HIV-1 Infected Subjects 153
3.5.1.1 Single-Dose Pharmacokinetics of TMC278 in HIV-1 Infected Subjects 153
3.5.1.2 Multiple-Dose Pharmacokinetics of TMC278 in HIV-1 Infected Subjects 154
3.5.1.3 Conclusions on TMC278 Pharmacokinetic Parameters Derived From Intensive Sampling in HIV-1 Infected Subjects 156
3.5.2 Population Pharmacokinetic Analysis of TMC278 in HIV-1 Infected Subjects 156
3.5.2.1 Population Pharmacokinetic Model for TMC278 157
3.5.2.2 Bayesian Estimation of Pharmacokinetic Parameters 157
3.5.2.3 Covariate Analysis of Population Pharmacokinetic Parameters 158
3.6 Comparison of Exposure to TMC278 Between Healthy Subjects and HIV-1 Infected Subjects 159
3.6.1 TMC278 Administered as Oral Solution 159
3.6.2 TMC278 Administered as Phase IIb Tablet 159
3.6.3 TMC278 Administered as Phase III Tablet 160
3.6.4 Conclusions 161
3.7 Effect of Intrinsic Factors 161
3.7.1 Effect of Age 162
3.7.2 Effect of Gender 162
3.7.3 Effect of Race 163
3.7.4 Effect of Body Weight and Body Mass Index 163
3.7.5 Effect of Estimated Glomerular Filtration Rate 164
3.7.6 Effect of Hepatitis B and/or C Coinfection Status 164
3.7.7 Effect of Hepatic Impairment 164
3.8 Effect of Extrinsic Factors 164
3.8.1 Impact of Concomitant Food Intake 165
3.8.2 Region 165
3.8.3 Background Medication in Highly Active Antiretroviral Therapy 165
3.8.4 Management of Known and Potential Drug-Drug Interactions 166
3.8.4.1 Potential for TMC278 to Affect Other Drugs 166
3.8.4.2 Potential for Other Drugs to Affect TMC278 168

3.8.4.3 Overview of Clinical Drug-Drug Interaction Trials 169
3.8.4.4 Established and Other Potentially Significant Drug Interactions 177
3.9 Pharmacodynamics - Efficacy 182
3.9.1 Phase IIa Proof-of-Principle Trials 182
3.9.1.1 Treatment-Naïve, HIV-1 Infected Subjects 182
3.9.1.2 Treatment-Experienced, HIV-1 Infected Subjects 182
3.9.2 Phase IIb Dose-Finding Trial 182
3.9.3 Phase III Trials 183
3.10 Pharmacokinetic/Pharmacodynamic Relationships for Efficacy Parameters 183
3.10.1 Phase IIa Proof-of-Principle Trials 183
3.10.1.1 Treatment-Naïve, HIV-1 Infected Subjects 183
3.10.1.2 Treatment-Experienced, HIV-1 Infected Subjects 183
3.10.2 Phase IIb Dose-Finding Trial 184
3.10.3 Phase III Trials 184
3.10.3.1 Pharmacokinetic Parameters and Virologic Response (Conventional Logistic Regression) 185
3.10.3.2 Modeling of Virologic Response and Change in $CD4^+$ Cell Count with Predictive Factors Using Generalized Additive Models 186
3.10.4 Conclusions on Relationships Between Pharmacokinetics and Efficacy Parameters 199
3.11 Pharmacokinetic/Pharmacodynamic Relationships for Safety Parameters 200
3.11.1 Relationships Between Pharmacokinetics and Adverse Events 200
3.11.2 Relationships Between Pharmacokinetics and Laboratory Parameters 200
3.11.3 Effect of TMC278 on QTcF Interval 200
3.11.3.1 Effect of TMC278 on QTcF Interval in Healthy Subjects 200
3.11.3.2 Effect of TMC278 on QTcF Interval in HIV-1 Infected Subjects 201
3.11.3.3 Pharmacokinetic/Pharmacodynamic Modeling and Simulation of the Effect of TMC278 on QTcF Prolongation in Healthy Subjects, Based on Pooled Data From Trials C131 and C152 201
3.12 Rationale for TMC278 Dose Selection in HIV-1 Infected Subjects 205
4 Special Trials 207
5 References 208
6 Appendices 211

LIST OF IN-TEXT TABLES

Table 1: Overview of Human Biomaterial Studies 24
Table 2: Overview of Trials Contributing Information to the Summary of Clinical Pharmacology Studies 26
Table 3: Number of Subjects Administered TMC278 in Phase I, II, and III Trials Included in the Summary of Clinical Pharmacology Studies 29
Table 4: Ongoing and Planned Phase I and Phase II Trials With TMC278 29
Table 5: Mean Plasma Protein Binding at Different Concentrations of TMC278 in Plasma of Healthy Men (Study NC112) 36
Table 6: Excretion of TMC278 and its Metabolites in Feces After a Single Oral Dose of 150 mg ^{14}C-TMC278 in Healthy Men (Study NC157; Trial C119) 39
Table 7: In Vitro Induction of Drug-Metabolizing Enzymes (Study NC186) 42
Table 8: In Vitro Inhibition of the Metabolism of Interacting Drugs by TMC278 (Study NC194) 44
Table 9: Pharmacokinetics of TMC278 and Total ^{14}C-Radioactivity in Plasma After Single-Dose Administration of 150 mg ^{14}C-Labelled TMC278 in Healthy Subjects (Trial C119) 45
Table 10: Pharmacokinetics of TMC278 After Administration at Single Doses of 12.5 to 50 mg in Healthy Subjects (Trial CDE-101) 48
Table 11: Ex Vivo Antiviral Activity of TMC278 After Administration at Single Doses of 12.5 to 50 mg in Healthy Subjects (Trial CDE-101) 48
Table 12: Pharmacokinetics of TMC278 After Administration at Single Doses of 50 to 300 mg in Healthy Subjects (Trial CDE-103) 50
Table 13: Ex Vivo Antiviral Activity of TMC278 After Administration at Single Doses of 50 to 300 mg in Healthy Subjects (Trial CDE-103) 50
Table 14: Pharmacokinetics of TMC278 After Administration at Multiple Doses of 25 to 150 mg q.d. in Healthy Subjects (Trial CDE-102) 53
Table 15: Ex Vivo Antiviral Activity of TMC278 After Administration at Multiple Doses of 25 to 150 mg q.d. in Healthy Subjects (Trial CDE-102) 54
Table 16: Pharmacokinetics of TMC278 After Administration at Multiple Doses of 25 to 150 mg q.d. in Healthy Subjects (Trial C103) 56
Table 17: Pharmacokinetics of TMC278 After Administration at Doses of 25, 50, 100, and 150 mg q.d. for 7 Days in HIV-1 Infected Subjects (Trial C201) 59
Table 18: Pharmacokinetics of TMC278 After Administration at Doses of 25, 50, and 150 mg q.d. for 7 Days in HIV-1 Infected Subjects (Trial C202) 62
Table 19: Pharmacokinetics of TMC278 After Administration at Doses of 25, 75, or 150 mg q.d. With 2 N(t)RTIs in HIV-1 Infected Subjects (Trial C204) 65
Table 20: Pharmacokinetics of Zidovudine and Zidovudine-Glucuronide at Week 4 After Administration of Zidovudine (300 mg b.i.d.) With Lamivudine (150 mg b.i.d.) and TMC278 at Doses of 25, 75, or 150 mg q.d. in HIV-1 Infected Subjects (Trial C204) 66
Table 21: Population Pharmacokinetic Estimates of TMC278 After Administration at Doses of 25, 75, or 150 mg q.d. With 2 N(t)RTIs in HIV-1 Infected Subjects (Trial C204) 67

Table 22: Pharmacokinetics of TMC278 After Administration of TMC278 25 mg q.d. With Tenofovir Disoproxil Fumarate/Emtricitabine in HIV-1 Infected Subjects (Trial C209, Pharmacokinetic Substudy) 71
Table 23: Population Pharmacokinetic Estimates of TMC278 After Administration of TMC278 25 mg q.d. With Tenofovir Disoproxil Fumarate/Emtricitabine in HIV-1 Infected Subjects (Trial C209) 71
Table 24: Pharmacokinetics of TMC278 After Administration of TMC278 25 mg q.d. With 2 N(t)RTIs in HIV-1 Infected Subjects (Trial C215, Pharmacokinetic Substudy)....74
Table 25: Population Pharmacokinetic Estimates of TMC278 After Administration of TMC278 25 mg q.d. With 2 N(t)RTIs in HIV-1 Infected Subjects (Trial C215) ...75
Table 26: Pharmacokinetics of TMC278 in Subjects With Mild Hepatic Impairment and Matched Healthy Control Subjects (Trial C130) 79
Table 27: Pharmacokinetics of TMC278 in Subjects With Moderate Hepatic Impairment and Matched Healthy Control Subjects (Trial C130)....80
Table 28: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Tenofovir Disoproxil Fumarate (Trial C104) 81
Table 29: Pharmacokinetics of Tenofovir After Administration of Tenofovir Disoproxil Fumarate With or Without TMC278 (Trial C104) 82
Table 30: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Didanosine (Trial C106)....83
Table 31: Pharmacokinetics of Didanosine After Administration of Didanosine With or Without TMC278 (Trial C106) 84
Table 32: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Lopinavir With Low-Dose Ritonavir (Trial C105) 85
Table 33: Pharmacokinetics of Lopinavir After Administration of Lopinavir With Low-Dose Ritonavir With or Without TMC278 (Trial C105) 85
Table 34: Pharmacokinetics of Ritonavir After Administration of Lopinavir With Low-Dose Ritonavir With or Without TMC278 (Trial C105) 86
Table 35: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Darunavir With Low-Dose Ritonavir (Trial C112) 87
Table 36: Pharmacokinetics of Darunavir After Administration of Darunavir With Low-Dose Ritonavir With or Without TMC278 (Trial C112)....88
Table 37: Pharmacokinetics of Ritonavir After Administration of Darunavir With Low-Dose Ritonavir With or Without TMC278 (Trial C112)....88
Table 38: Pharmacokinetics of TMC278 After Administration of TMC278 With at Least 2 N(t)RTIs and Efavirenz or Nevirapine (Trial C101) 90
Table 39: Pharmacokinetics of Efavirenz and Nevirapine After Administration With a Single Dose of TMC278 (Trial C101)....90
Table 40: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Rifampin (Trial C108)....92
Table 41: Pharmacokinetics of Rifampin and 25-Desacetylrifampin After Administration of Rifampin With or Without TMC278 (Trial C108)....92
Table 42: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Rifabutin (Trial C125)....94

Table 43: Pharmacokinetics of Rifabutin After Administration of Rifabutin With or Without TMC278 (Trial C125) 94
Table 44: Pharmacokinetics of 25-*O*-Desacetyl-Rifabutin After Administration of Rifabutin With or Without TMC278 (Trial C125) 95
Table 45: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Coadministration of Ketoconazole (Trial C127) 96
Table 46: Pharmacokinetics of Ketoconazole After Administration of Ketoconazole With or Without TMC278 (Trial C127) 97
Table 47: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without a Single Dose of Sildenafil (Trial C123) 98
Table 48: Pharmacokinetics of Sildenafil After a Single Dose With or Without TMC278 (Trial C123) 98
Table 49: Pharmacokinetics of *N*-Desmethyl Sildenafil After a Single Dose With or Without TMC278 (Trial C123) 99
Table 50: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Atorvastatin (Trial C116) 100
Table 51: Pharmacokinetics of Atorvastatin After Administration of Atorvastatin With or Without TMC278 (Trial C116) 101
Table 52: Pharmacokinetics of Atorvastatin Lactone After Administration of Atorvastatin With or Without TMC278 (Trial C116) 101
Table 53: Pharmacokinetics of 2-Hydroxy-Atorvastatin After Administration of Atorvastatin With or Without TMC278 (Trial C116) 102
Table 54: Pharmacokinetics of 4-Hydroxy-Atorvastatin After Administration of Atorvastatin With or Without TMC278 (Trial C116) 102
Table 55: Pharmacokinetics of the Total Hydroxy-Methylglutaryl Coenzyme A Reductase Activity After Administration of Atorvastatin With or Without TMC278 (Trial C116) 103
Table 56: Pharmacokinetics of TMC278 After Administration of TMC278 150 mg q.d. With (Trial C120) or Without (Trials C103, C114, C127, and C105) Ethinylestradiol and Norethindrone 104
Table 57: Pharmacokinetics of Ethinylestradiol After Administration of Ethinylestradiol and Norethindrone With or Without TMC278 150 mg q.d. (Trial C120) 105
Table 58: Pharmacokinetics of Norethindrone After Administration of Ethinylestradiol and Norethindrone With or Without TMC278 150 mg q.d. (Trial C120) 105
Table 59: Pharmacokinetics of TMC278 25 mg q.d. After Administration of TMC278 With (Trial C136) or Without (Trial C151) Ethinylestradiol and Norethindrone 107
Table 60: Pharmacokinetics of Ethinylestradiol After Administration of Ethinylestradiol and Norethindrone With or Without TMC278 25 mg q.d. (Trial C136) 107
Table 61: Pharmacokinetics of Norethindrone After Administration of Ethinylestradiol and Norethindrone With or Without TMC278 25 mg q.d. (Trial C136) 108
Table 62: Pharmacokinetics of TMC278 After Administration of TMC278 25 mg q.d. With (Trial C121) or Without (Trials C152 and C130) Methadone 109
Table 63: Pharmacokinetics of R(–) Methadone After Administration of Methadone With or Without TMC278 (Trial C121) 110
Table 64: Pharmacokinetics of S(+) Methadone After Administration of Methadone With or Without TMC278 (Trial C121) 110

Table 65: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Omeprazole (Trial C114)....112
Table 66: Pharmacokinetics of Omeprazole After Administration of Omeprazole With or Without TMC278 (Trial C114)....113
Table 67: Pharmacokinetics of 5-Hydroxy-Omeprazole After Administration of Omeprazole With or Without TMC278 (Trial C114)....114
Table 68: Pharmacokinetics of Omeprazole Sulfone After Administration of Omeprazole With or Without TMC278 (Trial C114)....115
Table 69: Pharmacokinetics of TMC278 After Administration of a Single Dose of TMC278 With or Without a Single Dose of Famotidine (Trial C140)....117
Table 70: Pharmacokinetics of Famotidine After a Single Dose With or Without a Single Dose of TMC278 (Trial C140)....118
Table 71: Pharmacokinetics of TMC278 After Administration of TMC278 With or Without Paracetamol (Trial C109)....119
Table 72: Pharmacokinetics of Paracetamol After Administration of Paracetamol With or Without TMC278 (Trial C109)....120
Table 73: Pharmacokinetics of Paracetamol Glucuronide and Paracetamol Sulfate After Administration of Paracetamol With or Without TMC278 (Trial C109)....120
Table 74: Pharmacokinetics of TMC278 After Administration of Multiple Doses of TMC278 With or Without a Single Dose of Chlorzoxazone (Trial C139)....122
Table 75: Pharmacokinetics of Chlorzoxazone After a Single Dose With or Without a Single Dose or Multiple Doses of TMC278 (Trial C139)....122
Table 76: Pharmacokinetics of 6-Hydroxy-Chlorzoxazone After a Single Dose With or Without a Single Dose or Multiple Doses of TMC278 (Trial C139)....123
Table 77: Pharmacokinetics of TMC278 on Days 1 and 11 After Administration of TMC278 at Doses of 75 mg and 150 mg q.d. in Healthy Subjects (Trial C131)....126
Table 78: Pharmacokinetics of Moxifloxacin After Administration of a Single 400 mg Dose on Day 12 in Healthy Subjects (Trial C131)....126
Table 79: Model-Based Predictions for Change in QTcF Interval (Day 11) at Various Plasma Concentrations of TMC278 for Difference Versus Placebo, Overall, and by Gender (Trial C131)....129
Table 80: Treatment-Induced Change in CYP3A4 Activity (Trial C131)....129
Table 81: Steady-State Pharmacokinetics of TMC278 After Administration of TMC278 at a Dose of 25 mg q.d. in Healthy Subjects (Trial C151)....132
Table 82: Steady-State Pharmacokinetics of TMC278 After Administration of TMC278 at a Dose of 25 mg q.d. in Healthy Subjects (Trial C152)....137
Table 83: Pharmacokinetics of Moxifloxacin After Administration of a Single 400 mg Dose in Healthy Subjects (Trial C152)....137
Table 84: Pharmacokinetics of Efavirenz on Day 11 After Administration at a Dose of 600 mg q.d. in Healthy Subjects (Trial C152)....138
Table 85: Across-Trial Summary of Pharmacokinetics of TMC278 After Single-Dose Administration of TMC278 Given as Oral Solution in Healthy Subjects (Trials CDE-C101 and CDE-C103)....148
Table 86: Pharmacokinetics of TMC278 After a Single Dose of TMC278 Given as the Phase IIb Tablet at Doses of 25 to 150 mg in Healthy Subjects (Trial C103)....148

Table 87: Pharmacokinetics of TMC278 After Single-Dose Administration of TMC278 Given as the Phase III Tablet at Doses of 25 to 150 mg in Healthy Subjects (Trials C145, C137, and C117) 149
Table 88: Pharmacokinetics of TMC278 After Administration of TMC278 as Oral Solution at Multiple Doses of 25 to 150 mg q.d. for 14 Days in Healthy Subjects (Trial CDE-102) 150
Table 89: Pharmacokinetics of TMC278 After Administration of TMC278 as the Phase IIb Tablet at Multiple Doses of 25 to 150 mg q.d. for 14 Days in Healthy Subjects (Trial C103) 151
Table 90: Pharmacokinetics of TMC278 After Administration of TMC278 as the Phase III Tablet at a Dose of 25 mg q.d. for 11 Days in Non-HIV-1 Infected Subjects (Trials C130, C152, C136, and C121) 152
Table 91: Pharmacokinetics of TMC278 After Single-Dose Administration of TMC278 as Oral Solution at Doses of 25 to 150 mg in HIV-1 Infected Subjects (Trials C201 and C202) 154
Table 92: Pharmacokinetics of TMC278 on Day 7 After Multiple-Dose Administration of TMC278 as Oral Solution at Doses of 25 to 150 mg q.d. in HIV-1 Infected Subjects (Trials C201 and C202) 155
Table 93: Pharmacokinetics of TMC278 After Multiple-Dose Administration of TMC278 as Phase III Tablet at Doses of 25 mg q.d. in HIV-1 Infected Subjects in Combination With Tenofovir Disoproxil Fumarate/Emtricitabine or 2 N(t)RTIs (Pooled Phase III Trials C209 and C215, Pharmacokinetic Substudies) 156
Table 94: Population Pharmacokinetic Estimates of TMC278 After Administration of TMC278 25 mg q.d. in HIV-1 Infected Subjects in Combination With Tenofovir Disoproxil Fumarate /Emtricitabine or 2 N(t)RTIs (Pooled Phase III Trials C209 and C215) 158
Table 95: Pharmacokinetics of TMC278 After Administration of TMC278 as Oral Solution at Doses of 25 and 150 mg q.d. in Healthy Subjects (Trial CDE-102) and HIV-1 Infected Subjects (Trials C201 and C202) 159
Table 96: Pharmacokinetics of TMC278 After Administration of TMC278 at Multiple Doses of 25 and 150 mg q.d. at Steady State in Healthy Subjects (Trial C103) and HIV-1 Infected Subjects (Trial C204, Pharmacokinetic Substudy) 160
Table 97: Pharmacokinetics of TMC278 After Administration of TMC278 at Multiple Doses of 25 mg q.d. at Steady State in Healthy Subjects (Trial C130 and C152) and in HIV-1 Infected Subjects (Trials C209 and C215, Pharmacokinetic Substudies) 161
Table 98: Drug Interactions: Pharmacokinetic Parameters for TMC278 in the Presence of Coadministered Drugs 169
Table 99: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of TMC278 171
Table 100: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Trials or Predicted Interaction 178
Table 101: Generalized Additive Models and Akaike Information Criterion Obtained at the End of Automated Step-Wise Searches for Predictive Factors of Virologic

Response (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) (Pooled Phase III Trials C209 and C215) 188

LIST OF IN-TEXT FIGURES

Figure 1: In Vitro Metabolic Pathways of TMC278 in Mice, Rats, Rabbits, Dogs, and Humans (Study NC102) 37
Figure 2: Metabolic Pathways of TMC278 After a Single Oral Dose of 150 mg ^{14}C-TMC278 in Healthy Men (Study NC157; Trial C119) 40
Figure 3: Mean Plasma Concentration-Time Profiles of TMC278 After Administration at Single Doses of 12.5 to 50 mg in Healthy Subjects (Trial CDE-101) 47
Figure 4: Mean Plasma Concentration-Time Profiles of TMC278 After Administration at Single Doses of 50 to 300 mg in Healthy Subjects (Trial CDE-103) 49
Figure 5: Mean Plasma Concentration-Time Profiles of TMC278 After Administration at Multiple Doses of 25 to 150 mg q.d. in Healthy Subjects (Trial CDE-102) 52
Figure 6: Correlation Between Individual Ex Vivo Antiviral Activity and Plasma Concentrations of TMC278 After Administration at Multiple Doses of 25 to 150 mg q.d. in Healthy Subjects (Trial CDE-102) 54
Figure 7: Mean Plasma Concentration-Time Profiles of TMC278 After Administration at Multiple Doses of 25 to 150 mg q.d. in Healthy Subjects (Trial C103) 55
Figure 8: Mean Plasma Concentration-Time Profiles of TMC278 After Administration at Doses of 25, 50, 100, and 150 mg q.d. in HIV-1 Infected Subjects (Trial C201) 58
Figure 9: Mean Plasma Concentration-Time Profiles of TMC278 After Administration at Doses of 25, 50, and 150 mg q.d. in HIV-1 Infected Subjects (Trial C202) 61
Figure 10: Proportion of Virologic Responders (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) by TMC278 AUC_{24h} Quartiles (ng.h/mL), at Weeks 48 and 96 (Trial C204) 69
Figure 11: Scatter-Plot of TMC278 AUC_{24h} by Virologic Response (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) at Week 48 (Trial C209) 72
Figure 12: Proportion of Virologic Responders (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) by TMC278 AUC_{24h} Quartiles (ng.h/mL) at Week 48 (Trial C209) 73
Figure 13: Scatter-Plot of TMC278 AUC_{24h} by Virologic Response (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) at Week 48 (Trial C215) 76
Figure 14: Proportion of Virologic Responders (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) by TMC278 AUC_{24h} Quartiles (ng.h/mL) at Week 48 (Trial C215) 77
Figure 15: Mean Plasma Concentration-Time Profiles of TMC278 on Days 1 and 11 After Administration at Doses of 75 mg and 300 mg q.d. in Healthy Subjects (Trial C131) 125
Figure 16: Time-Matched Difference Versus Placebo (Mean, 90% CI) in QTcF Interval for TMC278 at Doses of 75 and 300 mg q.d.: Day 1 (Left Panel) and Day 11 (Right Panel) (Trial C131) 127
Figure 17: Scatter Plots (With Smooth Splines) for Overall Data (Left Panel) and Data by Gender (Right Panel) for Difference Versus Placebo in QTcF Interval, Versus

Corresponding Time-Matched TMC278 Plasma Concentration on Day 11 (Trial C131) 128
Figure 18: Mean Plasma Concentration-Time Profile of TMC278 on Day 11 After Administration of TMC278 at a Dose of 25 mg q.d. in Healthy Subjects (Trial C151) 131
Figure 19: Time-Matched Change from Baseline (Mean, 90%CI) in QTcF Interval for TMC278 and TMC278 Placebo Administered at a Dose of 25 mg q.d. for 11 Days (Trial C151) 133
Figure 20: Scatter Plot of Time-Matched Change from Baseline in QTcF Interval Versus Corresponding Time-matched TMC278 Plasma Concentration on Day 11: TMC278 Only (Left Panel) and Pooled TMC278 and Placebo With Corresponding Zero TMC278 Concentration for Placebo (Right Panel) (Trial C151) 134
Figure 21: Mean Plasma Concentration-Time Profile of TMC278 on Day 11 After Administration at a Dose of 25 mg q.d. in Healthy Subjects (Trial C152) 136
Figure 22: Time-matched Difference Versus Placebo in QTcF Interval: TMC278 Panel (Left) and Efavirenz Panel (Right) (Trial C152) 139
Figure 23: Scatter Plots (With Smooth Lines) of Difference Versus Placebo in QTcF Interval on Day 11, Versus Corresponding Time-Matched Steady-State TMC278 (Left) and Efavirenz Concentrations (Right) (Trial C152) 139
Figure 24: Scatter Plots (With Smooth Lines) of Difference Versus Baseline in QTcF Interval on Day 11 Versus Corresponding Time-Matched Steady-State TMC278 (Left) and Efavirenz Concentrations (Right) (Trial C152) 140
Figure 25: Scatter Plots (With Smooth Line) of Maximum Difference Versus Placebo in QTcF Interval on Day 11 Versus Corresponding Time-Matched TMC278 (Left) and Efavirenz Concentrations (Right) (Trial C152) 141
Figure 26: Plot of Individual TMC278 AUC_{∞} Values Versus Mean Intragastric pH in the 2 to 4 Hours After TMC278 Administration Without Famotidine (Red Triangles) and When TMC278 Was Administered 2 Hours After Famotidine (Blue Squares) (Trial C140) 144
Figure 27: Scatter-Plot of TMC278 AUC_{24h} by Virologic Response (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) at Week 48 (Pooled Phase III Trials C209 and C215) 185
Figure 28: Proportion of Virologic Responders (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) by TMC278 AUC_{24h} Quartiles (ng.h/mL) at Week 48 (Pooled Phase III Trials C209 and C215) 186
Figure 29: Model-Predicted Probability of Virologic Response (Viral Load < 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) at Week 48 as a Function of the Predictive Factors Retained in the Final Generalized Additive Models (Blue Curves are Smooths Through the Data) (Pooled Phase III Trials C209 and C215) 190
Figure 30: Increase in Akaike Information Criterion From the Full Model of Virologic Response (< 50 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) as a Result of Deleting Each of the Predictive Factors, One by One (Pooled Phase III Trials C209 and C215) 191

Figure 31: Model-Predicted Probability of Virologic Response (Viral Load < 400 HIV-1 RNA Copies/mL) at Week 48 as a Function of the Predictive Factors Retained in the Final Generalized Additive Models (Blue Curves are Smooths Through the Data) (Pooled Phase III Trials C209 and C215).....192
Figure 32: Increase in Akaike Information Criterion From the Full Model of Virologic Response (< 400 HIV-1 RNA Copies/mL, TLOVR Non-VF Censored) as a Result of Deleting Each of the Predictive Factors, One by One (Pooled Phase III Trials C209 and C215).....193
Figure 33: Median (2.5% and 97.5% Percentiles) Prediction of the Likelihood of Response (TLOVR Non-VF Censored; < 50 HIV-1 RNA Copies/mL [Upper Panels], < 400 HIV-1 RNA Copies/mL [Lower Panels]) as a Function of TMC278 C_{0h} (Left Panels) and AUC_{24h} (Right Panels), Based on the Final Generalized Additive Models Fitted to 1000 Bootstrap Samples of the Original Data (Pooled Phase III Trials C209 and C215) 195
Figure 34: Model-Predicted Change in Absolute $CD4^+$ Cell Count From Baseline at Week 48 as a Function of the Predictive Factors Retained in the Final Generalized Additive Models (Blue Curves are Smooths Through the Data) (Pooled Phase III Trials C209 and C215) 197
Figure 35: Increase in Akaike Information Criterion From the Full Model of Change in Absolute $CD4^+$ Cell Count From Baseline as a Result of Deleting Each of the Predictive Factors, One by One (Pooled Phase III Trials C209 and C215).....198
Figure 36: Observed Change in Absolute $CD4^+$ Cell Count From Baseline as a Function of C_{0h} (Left Panel) and AUC_{24h} (Right Panel) of TMC278 (Blue Curves are Smooths Through the Data) (Pooled Phase III Trials C209 and C215).....199
Figure 37: Mean Increase in QTcF Interval (Left Panel) and Percentage of Subjects With QTcF Interval Increase From Baseline Above 30 ms (Blue Line) or Above 60 ms (Red Line) (Right Panel) Based on Simulations for 100000 Virtual Subjects (Simulation Based on Pooled Data From Trials C131 and C152).....202
Figure 38: Range of Upper Limits of the 90% Confidence Interval of the Mean Increase in QTcF Interval for 1000 Replicates of Each Exposure (C_{max}) Increase Relative to the C_{max} of TMC278 at 25 mg q.d. (Simulation Based on Pooled Data From Trials C131 and C152).....203
Figure 39: Probability of the Upper Limit of the 90% Confidence Interval for Change in QTcF Interval of Below 10 ms, as a Function of Increase in C_{max}, Based on 1000 Trial Replicates at Each C_{max} Increment of 25% (Simulation Based on Pooled Data From Trials C131 and C152).....204
Figure 40: Probability of the Upper Limit of the 90% Confidence Interval for Mean Change in QTcF Interval of Below 10 ms, as a Function of Increase in C_{max}, Based on 1000 Trial Replicates for C_{max} Increments of 5% (Simulation Based on Pooled Data From Trials C131 and C152).....205

LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADH	alcohol dehydrogenase
Ae	amount excreted
AE	adverse event
AIC	Akaike Information Criterion
ART	antiretroviral therapy
ARV	antiretroviral
AUC_{12h}, AUC_{24h}	area under the plasma concentration-time curve for the specified time period after dosing
AUC_{last}	area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration
AUC_{∞}	area under the plasma concentration-time curve from time of intake until infinity
$AUEC_{12h}$, $AUEC_{24h}$	area under the effect-time curve from 0 to specified time after dosing
AZT	zidovudine
b.i.d.	twice daily
BMI	body mass index
C_{0h}, C_{12h}	plasma concentrations at specified time after dosing
Caco-2	colon carcinoma-derived
$CD4^+$	cluster of differentiation 4
CI	confidence interval
CL	clearance
CL/F	apparent oral clearance
CL/F/kg	apparent oral clearance adjusted for body weight
CL_R	renal clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CRH	corticotropin-releasing hormone
CRR	clinical research report

$C_{ss,av}$	average steady-state plasma concentration (area under the plasma concentration-time curve/dosing interval at steady state)
CV	coefficient of variation
CYP	cytochrome P450
DAVG	time averaged difference
ddI	didanosine
DRV	darunavir
EC_{50}	50% effective concentration in cell-based assays
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
E_{max}	concentration for maximum antiviral effect
ENF	enfuvirtide
eq	equivalent
FC	fold change in EC_{50}
FDA	Food and Drug Administration
FI	fluctuation index
FTC	emtricitabine
GAM	generalized additive model
H_2	histamine-2
HCl	hydrochloride
HIV	human immunodeficiency virus
HLM	human liver microsome
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPLC	high-performance liquid chromatography
IC_{50}	50% inhibitory concentration
IQ	inhibitory quotient
K_i	inhibition constant
LC-MS/MS	liquid chromatography with tandem mass-spectrometry
LLOQ	lower limit of quantification
LPV	lopinavir
LS	least squares
mRNA	messenger ribonucleic acid

NNRTI	non-nucleoside reverse transcriptase inhibitor
non-VF	non-virologic failure
NRTI	nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OC	oral contraceptive
PEG	polyethylene glycol
P-gp	P-glycoprotein
PI	protease inhibitor
q.d.	once daily
QTcF	QT interval corrected by Fridericia's formula
RAM	resistance-associated mutation
RNA	ribonucleic acid
rtv	coadministered low-dose ritonavir
SD	standard deviation
$t_{1/2, term}$	terminal elimination half-life
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response
t_{max}	time to reach the maximum plasma concentration
TMC	Tibotec Medicinal Compound
UDPGT	uridine disphosphate glucuronosyltransferase

Trial/Study Naming Conventions

Throughout this document, "trials" is used for all clinical trials, and "studies" is used for all nonclinical studies. Throughout the development of Tibotec Medicinal Compound (TMC)278, different naming conventions were used for studies and trials, depending on when the study or trial was conducted. The first part of the study/trial identifier was one of the following:

- R278474-CDE- (used for the earlier trials)
- R278474-
- TMC278-
- TMC278-TiDP6- (used for the most recent trials in adults), or TMC278-TiDP38 (used for trials in the pediatric development program of TMC278)

All trials were given a suffix of a unique 3-digit number preceded by the letter C (for "clinical"), e.g., C201 or C209. The exception to this rule was the naming of trials R278474-CDE-101,

R278474-CDE-102, and R278474-CDE-103 and the ongoing trial TMC278-HIV1001. Similarly, all nonclinical studies were generally given a suffix of a unique 3-digit number preceded by the letters NC (for "nonclinical"), e.g., NC186. The pooled analysis is also referred to by a suffix of a unique 3-digit number preceded by the letter C; the first number being 9, i.e., the Phase III pooled analysis is referred to as C904.

In this document, studies and trials are given their full name where they are first mentioned (e.g., TMC278-TiDP6-C209, TMC278-NC186, R278474-CDE-101), but are subsequently referred to by a short name only (e.g., C209, NC186, CDE-101).

Table 1 and Table 2 list all nonclinical studies and clinical trials, respectively, described in this document, using both the full and abbreviated study and trial names.

1 BACKGROUND AND OVERVIEW

Tibotec Medicinal Compound (TMC)278, a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) selected for its high in vitro potency against wildtype human immunodeficiency virus type 1 (HIV-1) and NNRTI-resistant mutants. TMC278 investigated at a dose of 25 mg once daily (q.d.), with a background regimen of 2 nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs), in 2 registrational Phase III trials in antiretroviral (ARV) treatment-naïve HIV-1 infected subjects offers sustained efficacy and good tolerability.

During early development, TMC278 was referred to as R278474. This document will describe the product only as TMC278, except in the context of formulation batch numbers or full study/trial names. The international non-proprietary name and the United States adopted name is rilpivirine hydrochloride (HCl).

In the early clinical trials, TMC278 was formulated as the free base in an oral solution (R278474), but later the oral tablet formulation was developed containing TMC278 as the HCl salt (R314585). As a result, in later trials, TMC278 formulations were referred to as containing an amount of TMC278 as free base equivalent (eq). For consistency, the following convention is used throughout this document: "TMC278 **X** mg", means either a dose of **X** mg when the free base was used or **X** mg eq when the HCl salt was used.

The objective of this summary document is to provide an overview of the clinical pharmacology trials (mostly in healthy subjects) as well as the pharmacokinetic and pharmacokinetic/pharmacodynamic components of Phase II and Phase III trials (in HIV-1 infected subjects) conducted as part of the clinical development program for TMC278. In addition, nonclinical studies (generally conducted using human biomaterials) that assist in the interpretation of the pharmacokinetic data are summarized. Pharmacokinetic trials related to biopharmaceutics are discussed in detail in the Summary of Biopharmaceutic Studies and Associated Analytical Methods (refer to Module 2.7.1), and are referenced only briefly in this summary, where applicable.

The data presented in this summary support the following conclusions for the pharmacokinetics and pharmacokinetic/pharmacodynamic relationships of TMC278:

- TMC278 is orally available; with the maximum plasma concentration (C_{max}) attained approximately 4 hours after administration. The rate of TMC278 absorption is not influenced by the dose.
- In healthy subjects, the exposure to TMC278 administered as a tablet increases dose proportionally across a dose range of 25 to 150 mg q.d. In HIV-1 infected subjects, a less than dose-proportional increase in exposure to TMC278 was observed.
- The exposure to TMC278 is approximately 40% lower under fasting conditions. TMC278 should therefore be administered with a meal to ensure optimal absorption and exposure.
- The inter-individual variability of TMC278 pharmacokinetic parameters is generally low or moderate, and independent of the dose administered.
- The mean terminal elimination half-life ($t_{1/2, term}$) of TMC278 is approximately 45 to 50 hours.

- TMC278 is on average 99.7% bound to proteins in plasma, mainly to albumin.
- TMC278 is predominantly excreted in feces (85.1%). There is negligible renal excretion of TMC278.
- The exposure to TMC278 was generally lower in HIV-1 infected subjects compared to healthy subjects.
- There is no clinically relevant effect of intrinsic factors (age, gender, race, body weight, estimated glomerular filtration rate [eGFR], and hepatitis B and/or C coinfection status) on the pharmacokinetics of TMC278.
- No dose adjustment of TMC278 is needed in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the exposure to TMC278 was not studied.
- The oral bioavailability of TMC278 decreases with increasing intragastric pH. Drugs that alter intragastric pH should not be coadministered with TMC278 unless alternative dosing regimens are available.
- Cytochrome P450 (CYP)3A enzymes have a predominant role in the metabolism of TMC278.
- TMC278 at a dose of 25 mg q.d. does not have a clinically relevant effect on the exposure to coadministered drugs. Mild induction of CYP3A and CYP2C19 observed at higher doses of TMC278 is unlikely to be of clinical importance at the recommended dose of TMC278 25 mg q.d.
- The exposure to TMC278 is increased by inhibition of CYP3A enzyme activity. TMC278 and CYP3A inhibitors evaluated in drug-drug interaction trials with TMC278 can be coadministered without dose adjustments.
- The exposure to TMC278 is decreased by induction of CYP3A enzyme activity. CYP3A inducers should not be coadministered with TMC278.
- In an analysis using generalized additive models (GAMs) to evaluate the impact of various potentially predictive factors on efficacy parameters, adherence was found to be the most important predictive factor for virologic response (viral load < 50 HIV-1 ribonucleic acid [RNA] copies/mL, time to loss of virologic response [TLOVR] non-virologic failure [non-VF] censored) followed by exposure to TMC278 and baseline viral load.
- TMC278 at the recommended dose of 25 mg q.d. did not demonstrate any clinically relevant effect on the QT interval corrected by Fridericia's formula (QTcF) in a thorough QT trial in healthy subjects. A positive TMC278 plasma concentration-relationship with changes in the QTcF interval was seen with TMC278 75 mg q.d. and 300 mg q.d, but not with TMC278 at the recommended dose of 25 mg q.d., indicating that the potential for prolongation of the QTcF interval is dose- and plasma concentration-dependent.
- There was no relationship between the exposure to TMC278 and either the occurrence of adverse events or clinically relevant changes in laboratory parameters of interest.

1.1 HUMAN BIOMATERIAL STUDIES

A total of 9 human biomaterial studies provided supporting information on the clinical pharmacology of TMC278. These studies investigated transport characteristics, P-glycoprotein (P-gp) inhibition, protein binding, in vivo metabolism, CYP enzymes involved in the metabolism of TMC278, and the in vitro drug-drug interaction potential of TMC278. The studies provide information on the absorption (colon carcinoma-derived [Caco-2] cells), distribution (in plasma), and metabolism (in hepatocytes, liver subcellular fractions, urine, feces, plasma, liver microsomes, and with P450 probe substrates) of TMC278. A tabular overview of human biomaterial studies presented in this document is available in Table 1. Further details are available in Section 2.1 as well as in Sections 3.1, 3.2, and 3.3 and in the Nonclinical Summary (refer to Module 2.6.4 Pharmacokinetics Written Summary).

Table 1: Overview of Human Biomaterial Studies

Nonclinical Study	Objective	Human Biomaterial	TMC278 Concentration [a]	Location of Study Report
Absorption				
TMC278-NC104 (NC104) (Section 2.1.1)	Transport characteristics and P-gp inhibition	Colon carcinoma-derived (Caco-2) cells	3, 10, 30, 100, 300 µM (1099, 3664, 10993, 36642, 109926 ng/mL)	Module 4.2.2.2 TMC278-NC104
Distribution				
TMC278-NC112 (NC112) (Section 2.1.2)	Protein binding	Plasma	10, 100, 300, 1000, 3000 ng/mL (0.03, 0.27, 0.82, 2.73, 8.19 µM)	Module 4.2.2.3 TMC278-NC112
Metabolism				
TMC278-NC102 (NC102) (Section 2.1.3.1)	In vitro metabolism of ^{14}C-TMC278	Hepatocytes, liver subcellular fractions	5 µM (1832 ng/mL)	Module 4.2.2.4 TMC278-NC102
TMC278-TiDP6-NC157 (NC157; clinical trial TMC278-C119) (Section 2.1.3.2)	In vivo metabolism of ^{14}C-TMC278	Urine, feces, plasma	C_{max} in plasma: 602.8 ng/mL (1.65 µM)	Module 4.2.2.4 TMC278-NC157
TMC278-NC141 (NC141) (Section 2.1.3.3)	Characterization of CYP enzymes involved in metabolism of TMC278, and determination of kinetics of TMC278 metabolism	Liver microsomes	0.5, 1, 3, 5, 7.5, 10, 15, 20, 30, 50 µM (183, 366, 1099, 1832, 2748, 3664, 5496, 7328, 10993, 18321 ng/mL)	Module 4.2.2.4 TMC278-NC141
R278474-FK4123 (FK4123) (Section 2.1.3.4)	The effect of TMC278 on the CYP activity	Liver microsomes, P450 probe substrates selective towards human CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP4A	0, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 µM (0, 11, 37, 110, 366, 1099, 3664, 10993, 36642 ng/mL)	Module 4.2.2.4 TMC278-FK4123
TMC278-NC186 (NC186) (Section 2.1.3.5)	Potential of TMC278 to induce CYP enzyme activities	Cryopreserved human hepatocytes	2.5, 10, 25 µM (916, 3664, 9161 ng/mL)	Module 4.2.2.4 TMC278-NC186

Table 1: Overview of Human Biomaterial Studies, Cont'd

Nonclinical Study	Objective	Human Biomaterial	TMC278 Concentration [a]	Location of Study Report
TMC278-TiDP6-NC283 (NC283) (Section 2.1.3.6)	Potential inhibitory effect of TMC278 on paclitaxel and S-warfarin metabolism	Liver microsomes	0.1, 0.3, 1, 3, 10, 30, 100, 200, 300 µM (37, 110, 366, 1099, 3664, 10993, 36642, 73284, 109926 ng/mL)	Module 4.2.2.4 TMC278-NC283
TMC278-NC194 (NC194) (Section 2.1.3.7)	Potential inhibitory effect of TMC278 on metabolism of sertraline, paroxetine, clarithromycin, sildenafil, 17α-ethinylestradiol, omeprazole, S-mephenytoin, ABC, norethindrone and chlorzoxazone	Liver microsomes, liver cytosol	0, 0.3, 1, 3, 10, 30 µM (0, 110, 366, 1099, 3664, 10993 ng/mL)	Module 4.2.2.6 TMC278-NC194

ABC = abacavir.

[a] Concentration data in parentheses have been calculated from data presented in the clinical research report.

1.2 CLINICAL PHARMACOLOGY TRIALS

The pharmacokinetics of TMC278 were assessed as either a primary or secondary objective of all Phase I, II, and III trials conducted to date. Non-HIV infected adults were enrolled in all Phase I trials with the exception of 1 Phase I trial in HIV-1 infected adults taking at least 2 N(t)RTIs (R278474-C101 [C101]). One Phase I trial was conducted in subjects with mildly or moderately impaired hepatic function and matched healthy subjects (TMC278-TiDP6-C130 [C130]), and 1 Phase I trial was conducted in non-HIV infected subjects on stable methadone maintenance therapy (TMC278-TiDP6-C121 [C121]). HIV-1 infected adults were enrolled in all Phase II and III trials.

Pharmacokinetic/pharmacodynamic relationships for antiviral activity or efficacy as well as safety parameters were investigated in the 2 proof-of-principle trials (R278474-C201 [C201] and R278474-C202 [C202]) as well as in the dose-finding Phase IIb trial (TMC278-C204 [C204]) and in the 2 registrational Phase III trials (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]).

The clinical trials summarized in this document are listed in Table 2, together with the TMC278 dosage form, formulation number, and dose, and the dosage form of any coadministered drugs. Further information on these trials is available in Appendix 2.7.2.5, Module 2.7.2 Appendix: Tabulated Summary of Completed Clinical Pharmacology Studies - Pharmacokinetics, Module 2.7.2 Appendix: Tabulated Summary of Completed Clinical Pharmacology Studies - Drug-Drug Interaction, and Module 2.7.3 Appendix: Tabulated Summary of Clinical Efficacy and Safety Studies.

Table 2: Overview of Trials Contributing Information to the Summary of Clinical Pharmacology Studies

Clinical Trial	TMC278			Dosage Form of Coadministered or Control Drugs
	Dosage Form [a]	Formulation Number	Dose	
Mass-Balance of TMC278 in Healthy Subjects				
TMC278-C119 (C119) (Section 2.2)	25 mg/mL oral solution (^{14}C-labeled TMC278)		150 mg	NA
Single-Dose Pharmacokinetics of TMC278 in Healthy Subjects				
R278474-CDE-101 (CDE-101) (Section 2.3.1)	25 mg/mL oral solution	R278474 F002	12.5, 25, and 50 mg	NA
R278474-CDE-103 (CDE-103) (Section 2.3.2)	25 mg/mL oral solution	R278474 F002	50, 100, 200, and 300 mg	NA
Multiple-Dose Pharmacokinetics of TMC278 in Healthy Subjects				
R278474-CDE-102 (CDE-102) (Section 2.4.1)	25 mg/mL oral solution	R278474 F002	25, 75, and 150 mg	NA
TMC278-C103 (C103) (Section 2.4.2)	25 and 100 mg Phase IIb tablets	R314585 F001 and R314585 F002	25, 50, 100, and 150 mg	NA
Multiple-Dose Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Relationships in HIV-1 Infected Subjects				
Phase IIa (Proof-of-Principle) Trials				
R278474-C201 (C201) (Section 2.6.1.1)	25 mg/mL oral solution	R278474 F002	25, 50, 100, and 150 mg	NA
R278474-C202 (C202) (Section 2.6.1.2)	25 mg/mL oral solution	R278474 F002	25, 50, and 150 mg	2 or more N(t)RTIs with or without ENF
Phase IIb (Dose-Finding) Trials				
TMC278-C204 (C204) (Section 2.6.2)	25, 50, and 100 mg Phase IIb tablets	R314585 F001, R314585 F003, and R314585 F002	25, 75, and 150 mg	2 investigator-selected N(t)RTIs: either AZT/3TC or TDF/FTC control: EFV
Phase III Trials				
TMC278-TiDP6-C209 (C209) (Section 2.6.3.1)	25 mg Phase III tablet	R314585 F006	25 mg	2 fixed N(t)RTIs: TDF/FTC control: EFV
TMC278-TiDP6-C215 (C215) (Section 2.6.3.2)	25 mg Phase III tablet	R314585 F006	25 mg	2 investigator-selected N(t)RTIs: either ABC/3TC, AZT/3TC, or TDF/FTC Control: EFV
Effect of Intrinsic Factors				
TMC278-TiDP6-C130 (C130) (Section 2.7)	25 mg Phase III tablet	R314585 F006	25 mg	NA

Table 2: Overview of Trials Contributing Information to the Summary of Clinical Pharmacology Studies, Cont'd

Clinical Trial	TMC278			Dosage Form of Coadministered or Control Drugs
	Dosage Form [a]	Formulation Number	Dose	
Effect of Extrinsic Factors: Concomitant Administration of TMC278 with Other Drugs				
Administration of TMC278 with Other Antiretrovirals (Healthy Subjects)				
TMC278-C104 (C104) (Section 2.8.1.1)	25 and 100 mg Phase IIb tablets	R314585 F001 and R314585 F002	150 mg	TDF (Viread®): 300 mg tablet
TMC278-C106 (C106) (Section 2.8.1.2)	25 and 100 mg Phase IIb tablets	R314585 F001 and R314585 F002	150 mg	ddI (Videx EC®): 400 mg enteric coated capsule
TMC278-C105 (C105) (Section 2.8.1.3)	25 and 100 mg Phase IIb tablets	R314585 F001 and R314585 F002	150 mg	LPV/rtv (Kaletra®): 133.3/33.3 mg capsule
TMC278-C112 (C112) (Section 2.8.1.4)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	DRV (Prezista®): 400 mg tablet Ritonavir (Norvir®): 100 mg capsule
Administration of TMC278 with Other Antiretrovirals (HIV-1 Infected Subjects)				
R278474-C101 (C101) (Section 2.8.2.1)	25 mg/mL oral solution	R278474 F002	50 mg	EFV (Sustiva®): 200 mg capsule NVP (Viramune®): 200 mg tablet
Administration of TMC278 with Drugs other than Antiretrovirals (Healthy Subjects)				
R278474-C108 (C108) (Section 2.8.3.1)	25 mg/mL oral solution	R278474 F002	150 mg	Rifampin (Rifadin®): 300 mg capsule
TMC278-C125 (C125) (Section 2.8.3.2)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Rifabutin (Mycobutin®): 150 mg capsule
TMC278-C127 (C127) (Section 2.8.3.3)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Ketoconazole (Nizoral®): 200 mg tablet
TMC278-TiDP6-C123 (C123) (Section 2.8.3.4)	75 mg Phase III tablet	R314585 F008	75 mg	Sildenafil (Viagra®): 50 mg tablet
TMC278-C116 (C116) (Section 2.8.3.5)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Atorvastatin (Sortis®): 40 mg tablet
TMC278-C120 (C120) (Section 2.8.3.6)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Ethinylestradiol/norethindrone (Ortho-Novum®): 35 µg/1.0 mg tablet
TMC278-TiDP6-C136 (C136) (Section 2.8.3.7)	25 mg Phase III tablet	R314585 F006	25 mg	Ethinylestradiol/norethindrone (Ovysmen®): 35 µg/1.0 mg tablet
TMC278-TiDP6-C121 (C121) (Section 2.8.3.8)	25 mg Phase III tablet	R314585 F006	25 mg	Methadone (Symoron®): 60 to 100 mg (individualized dose)
TMC278-C114 (C114) (Section 2.8.3.9)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Omeprazole (Losec®): 20 mg tablet

Table 2: Overview of Trials Contributing Information to the Summary of Clinical Pharmacology Studies, Cont'd

Clinical Trial	TMC278			Dosage Form of Coadministered or Control Drugs
	Dosage Form [a]	Formulation Number	Dose	
TMC278-C140 (C140) (Section 2.8.3.10)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Famotidine (Pepdine®): 40 mg tablet
TMC278-C109 (C109) (Section 2.8.3.11)	25 and 100 mg Phase IIb tablets	R314585 F001 and R314585 F002	150 mg	Paracetamol (acetaminophen, Perdolan®): 500 mg tablet
TMC278-C139 (C139) (Section 2.8.3.12)	50 and 100 mg Phase IIb tablets	R314585 F003 and R314585 F002	150 mg	Chlorzoxazone (Parafon Forte® DSC): 500 mg caplet (capsule shaped tablet)
Effect of TMC278 on ECG (Healthy Subjects)				
TMC278-TiDP6-C131 (C131) (Section 2.9.1)	75 mg Phase III tablet	R314585 F008	75 and 300 mg	Moxifloxacin (Avelox®): 400 mg film-coated tablet (overencapsulated in hard-gelatin capsules with microcrystalline cellulose spheres as filler)
TMC278-TiDP6-C151 (C151) (Section 2.9.2)	25 mg Phase IIb tablet	R314585 F001	25 mg	Moxifloxacin (Avelox®): 400 mg film-coated tablet (overencapsulated in hard-gelatin capsules with microcrystalline cellulose spheres as filler)
TMC278-TiDP6-C152 (C152) (Section 2.9.3)	25 mg Phase III tablet	R314585 F006	25 mg	Moxifloxacin (Avelox®): 400 mg film-coated tablet (overencapsulated in hard-gelatin capsules with microcrystalline cellulose spheres as filler) EFV (Sustiva®): 600 mg film-coated tablet (de-inked and over-coated)

3TC = lamivudine; AZT = zidovudine; ddI = didanosine; DRV = darunavir; ECG = electrocardiogram; EFV = efavirenz; ENF = enfuvirtide; FTC = emtricitabine; LPV = lopinavir; NA = not applicable; NVP = nevirapine; rtv = coadministered low-dose ritonavir; TDF = tenofovir disoproxil fumarate.

[a] The qualitative composition of the Phase III tablet formulations (collectively referred to as Phase III tablet) is very similar to the Phase IIb tablet formulations (collectively referred to as Phase IIb tablet), refer to Module 2.7.1/Section 1.3 for further details. Apart from the debossing, the intended commercial formulation will be identical to the 25 mg Phase III tablet.

Data from 31 Phase I, II, and III trials, in which 1607 healthy or HIV-1 infected subjects were administered TMC278, are summarized in this document (see Table 3). Data from a further 4 Phase I trials are summarized in Module 2.7.1.

Table 3: Number of Subjects Administered TMC278 in Phase I, II, and III Trials Included in the Summary of Clinical Pharmacology Studies

Type of Trial	Number of Trials	Population	Number of Subjects
Phase I, single-dose	2 (CDE-101, CDE-103)	Healthy subjects	42 (18+24)
Phase I, mass-balance	1 (C119)	Healthy subjects	6
Phase I, multiple-dose	2 (CDE-102, C103)	Healthy subjects	66 (18+48)
Phase I, effect of hepatic impairment	1 (C130)	Subjects with mild or moderate hepatic impairment and matched healthy subjects	32
Phase I, drug-drug interaction	16 (C104, C106, C105, C112, C108, C125, C127, C123, C116, C120, C136, C121, C114, C140, C109, C139)	Healthy subjects	284 (16+26+16+16+ 16+18+16+16+ 16+16+18+13+ 16+24+16+25)
Phase I, drug-drug interaction	1 (C101)	HIV-1 infected subjects	15
Phase I, effect on ECG	3 (C131, C151, C152)	Healthy subjects	125 (41+24+60)
Phase IIa	2 (C201, C202)	HIV-1 infected subjects	72 (36+36)
Phase IIb	1 (C204)	HIV-1 infected subjects	279
Phase III	2 (C209, C215)	HIV-1 infected subjects	686 (346+340)
Total	**31**		**1607**

Source: clinical research reports

Ongoing and planned Phase I and Phase II trials with TMC278 are listed in Table 4. These trials are not part of the current submission.

Table 4: Ongoing and Planned Phase I and Phase II Trials With TMC278

Trial Number	Interacting Drug or Special Population	Status [a]
TMC278-TiDP6-C154	Healthy subjects, TMC278 with and without coadministration of omeprazole	Ongoing
TMC278-HIV1001	Healthy subjects, TMC278 administered before and after a switch from EFV	Ongoing
TMC278-TiDP38-C213	HIV-1 infected adolescents (12 to 18 years of age)	Planned
TMC278-TiDP38-C220	HIV-1 infected children (up to 12 years of age)	Planned

[a] Status as of March 2010.
Source: Module 2.7.3 Appendix: Tabular Overview of Ongoing and Planned Trials with TMC278

1.3 BIOANALYTICAL METHODS

The bioanalytical methods used for the determination of TMC278 concentrations during the clinical development program for TMC278 are described in Module 2.7.1/Section 1.2. An overview of the validated analytical methods for TMC278 as well as all other analytes in the individual clinical trials is available in Module 2.7.1/Appendix 2.7.1.2.

1.4 ABSORPTION

Human Caco-2 cells were used as an in vitro model to investigate the bi-directional transepithelial transport characteristics of ^{14}C-TMC278 (TMC278-NC104 [NC104]).

The absolute bioavailability of TMC278 has not been investigated because an acceptable intravenous formulation is not available. In particular, an intravenous formulation of TMC278 is challenging to produce due to the poor solubility of the TMC278 drug substance (refer to

Module 3.2.P.2.1 Drug Substance/Section 1 and Module 3.2.P.2.2 Physicochemical and Biological Properties/Section 2).

In clinical trials, the impact of concomitant food intake on the absorption and bioavailability of TMC278 after oral administration was investigated in 2 clinical trials (R278474-C102 [C102] and TMC278-TiDP6-C137 [C137], refer to Module 2.7.1/Section 3.2). Furthermore, the effect of increased intragastric pH was explored in trials TMC278-C114 (C114) and TMC278-C140 (C140), in which TMC278 150 mg q.d. was coadministered with omeprazole and famotidine, respectively. An additional trial (TMC278-TiDP6-C154 [C154]) is being conducted to investigate the interaction between TMC278 25 mg q.d. and omeprazole, as well as possible strategies to circumvent the potential interaction, to provide more informed guidance for coadministration of TMC278 and proton pump inhibitors.

The absorption of TMC278 is discussed in Section 3.1.

1.5 DISTRIBUTION

The plasma protein binding of TMC278 was investigated in an in vitro study (TMC278-NC112 [NC112]). The blood to plasma ratios of ^{14}C-radioactivity after a single oral dose of 150 mg ^{14}C-TMC278 were investigated in a mass-balance trial (TMC278-C119 [C119]). The distribution of TMC278 into compartments other than plasma (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

The distribution of TMC278 is discussed in Section 3.2.

1.6 METABOLISM AND EXCRETION

The in vitro metabolism of TMC278 was studied in hepatocytes and liver subcellular fractions of humans and various animal species. The in vivo metabolism of ^{14}C-TMC278 was studied in feces, urine, and plasma collected from healthy male subjects after a single oral dose of 150 mg TMC278 in a mass-balance trial (C119).

The role of CYP enzymes in the in vitro metabolism of TMC278 was studied using different CYP reaction phenotyping approaches (study TMC278-NC141 [NC141]). The in vitro effect of TMC278 on CYP activity was investigated in pooled human liver microsomes (HLMs) (study R278474-FK4123 [FK4123]) and the in vitro potential to induce CYP enzyme activities was investigated in cryopreserved human hepatocytes (study TMC278-NC186 [NC186]).

The metabolism and excretion of TMC278 are discussed in Section 3.3. The results of the nonclinical studies investigating the metabolism and excretion of TMC278 are discussed in detail in the Nonclinical Summary (Module 2.6.4 Pharmacokinetics Written Summary).

1.7 PHARMACOKINETICS OF TMC278 AFTER SINGLE- AND MULTIPLE-DOSE ADMINISTRATION IN HEALTHY SUBJECTS

Data on the single-dose pharmacokinetics of TMC278 in healthy subjects with the oral solution that was used in the early Phase I and Phase IIa trials are available from single-dose escalation trials at doses of 12.5 to 50 mg (R278474-CDE-101 [CDE-101]) and 50 to 300 mg (R278474-CDE-103 [CDE-103]).

After administration of the Phase IIb tablet, single-dose pharmacokinetic data were obtained after the first administration of TMC278 at doses of 25 to 150 mg in the multiple-dose trial TMC278-C103 (C103). The single-dose pharmacokinetics of TMC278 administered as the Phase III tablet were obtained after single-dose administration of TMC278 in trials TMC278-TiDP38-C145 (C145; 25 mg), C137 (75 mg), and TMC278-C117 (C117; 100 and 150 mg).

Data on the multiple-dose pharmacokinetics of TMC278 in healthy subjects are described from a multiple-dose escalation trial (R278474-CDE-102 [CDE-102]) with the oral solution (25 to 150 mg q.d.) and a multiple-dose trial (C103) with the Phase IIb tablet (25 to 150 mg q.d.). Data on the multiple dose-pharmacokinetics of TMC278 25 mg q.d. with the Phase IIb tablet are also available from a pilot QT/QTc trial (TMC278-TiDP6-C151 [C151]). Multiple-dose pharmacokinetics of TMC278 in healthy subjects with the Phase III tablet (25 mg q.d.) are described from a thorough QT/QTc trial (TMC278-TiDP6-C152 [C152]) and a hepatic impairment trial (C130), as well as from 2 drug-drug interaction trials in which TMC278 was coadministered with ethinylestradiol and norethindrone (TMC278-TiDP6-C136 [C136]) and methadone (C121). Multiple-dose pharmacokinetics of TMC278 in healthy subjects are also available from a thorough QT/QTc trial (TMC278-TiDP6-C131 [C131]) with the Phase III 75 mg tablet at doses of 75 and 300 mg q.d.

The single- and multiple-dose pharmacokinetics of TMC278 in healthy subjects are discussed in Section 3.4.1 and Section 3.4.2, respectively.

1.8 PHARMACOKINETICS OF TMC278 AFTER SINGLE- AND MULTIPLE-DOSE ADMINISTRATION IN HIV-1 INFECTED SUBJECTS

Most data in HIV-1 infected subjects are from multiple-dose administration of TMC278: with the Phase IIb tablet at doses of 25, 75, and 150 mg q.d. in the Phase IIb trial (C204) and with the Phase III tablet of TMC278 (25 mg q.d.) in the 2 Phase III trials (C209 and C215).

Limited single- and multiple-dose data with the oral solution (25 to 150 mg) are available from the 2 Phase IIa proof-of-principle trials in treatment-naïve subjects (C201) and in treatment-experienced subjects (C202).

Population pharmacokinetic analyses of TMC278 exposure in HIV-1 infected subjects are available from the Phase IIb trial, and from the Phase III trials.

The single- and multiple-dose pharmacokinetics of TMC278 derived from intensive sampling in HIV-1 infected subjects are discussed in Section 3.5.1, and the population pharmacokinetic analyses based on sparse sampling are discussed in Section 3.5.2.

1.9 COMPARISON OF EXPOSURE TO TMC278 BETWEEN HEALTHY SUBJECTS AND HIV-1 INFECTED SUBJECTS

A comparison of the exposure to TMC278 between healthy subjects and HIV-1 infected subjects is based on across-trial comparisons of:

- Non-compartmental pharmacokinetic analyses of TMC278 plasma concentrations (intensive sampling) after administration of different formulations of TMC278;
- The Phase IIb and Phase III population pharmacokinetic analyses (see Section 3.6).

1.10 EFFECT OF INTRINSIC FACTORS

In HIV-1 infected subjects, intrinsic factors that have been considered for their potential effect on the pharmacokinetics of TMC278 include age, gender, race, body weight, creatinine clearance (using baseline eGFR), and hepatitis B and/or C coinfection status. The potential impact of these factors was evaluated in the Phase IIb trial C204 and in the Phase III trials C209 and C215, using univariate and multivariate analysis of covariance (ANCOVA), and has also been explored using covariate modeling in the population pharmacokinetic analysis of TMC278 for the pooled data from trials C209 and C215.

A specific trial (C130) in non-HIV-1 infected subjects was conducted to investigate the effect of mild and moderate hepatic impairment on the pharmacokinetics of TMC278.

In view of the negligible renal excretion of TMC278 (see Section 3.3.2), a trial to investigate the exposure to TMC278 in subjects with renal impairment has not been conducted.

The effect of intrinsic factors is discussed in Section 3.7.

1.11 EFFECT OF EXTRINSIC FACTORS

Extrinsic factors that have been considered for their potential effect on the pharmacokinetics of TMC278 include the impact of concomitant food intake, region, background medication, and drug-drug interactions. The potential impact of these factors was evaluated in the Phase IIb and Phase III trials, except for the impact of concomitant food intake and the drug-drug interactions, which were evaluated in specific trials.

The effect of extrinsic factors is discussed in Section 3.8.

1.11.1 Impact of Concomitant Food Intake

The effect of concomitant food intake on the oral bioavailability of TMC278 administered as a tablet was investigated in 2 clinical trials (C102 using the 100 mg Phase IIb tablet and C137 using the 75 mg Phase III tablet).

The effect of concomitant food intake is discussed in Section 3.8.1.

1.11.2 Drug-Drug Interactions

Against the background of the in vitro findings and theoretical considerations for potential drug-drug interactions (see Section 3.3.1), 17 clinical trials have been conducted to evaluate the effects of coadministration of TMC278 with various classes of drugs, including CYP3A substrates, inducers, or inhibitors, a CYP2E1 substrate, and drugs that alter intragastric pH. The drugs chosen are either ARVs or non-ARV drugs that are frequently used by HIV-1 infected subjects. An overview of the results obtained is available in Table 98 for the effect of other drugs on the pharmacokinetic parameters of TMC278, and in Table 99 for the effect of TMC278 on the pharmacokinetic parameters of the coadministered drugs.

The clinical drug-drug interaction trials are discussed in Section 3.8.4.

1.12 PHARMACODYNAMICS - EFFICACY

The antiviral activity or efficacy results of TMC278 from the Phase IIa proof-of principle trials (C201 and C202), the Phase IIb dose-finding trial C204, and the Phase III trials (C209 and C215) are briefly summarized in Section 3.9. The results of the efficacy analyses for TMC278 are discussed in detail in the Summary of Clinical Efficacy (refer to Module 2.7.3).

1.13 PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR EFFICACY PARAMETERS

Pharmacokinetic data for TMC278 are available from all trials in HIV-1 infected subjects. The relationship between TMC278 exposure and short-term or long-term antiviral activity was evaluated in each of the following trials:

- 2 Phase IIa proof-of-principle trials in treatment-naïve subjects (C201) and in treatment-experienced subjects (C202) who were treated with TMC278 at doses of 25 to 150 mg q.d. for 7 days (see Section 3.10.1);
- 1 Phase IIb dose-finding trial C204 in treatment-naïve subjects who were treated with TMC278 at doses of 25, 75, or 150 mg q.d. (from analyses at Weeks 48 and 96) (see Section 3.10.2);
- 2 Phase III trials (C209 and C215) in treatment-naïve subjects who were treated with TMC278 25 mg q.d. (from analysis at Week 48) (see Section 3.10.3).

1.14 PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR SAFETY PARAMETERS

1.14.1 Relationships Between Pharmacokinetics and Adverse Events

The relationship between the exposure to TMC278 and the occurrence of adverse events in HIV-1 infected subjects was assessed over a period of 96 weeks in the Phase IIb trial C204 (25, 75, or 150 mg q.d.) and over a period of 48 weeks in the Phase III trials C209 and C215 (25 mg q.d.) (see Section 3.11.1).

1.14.2 Relationships Between Pharmacokinetics and Laboratory Parameters

The relationship between the exposure to TMC278 and changes from baseline in laboratory parameters of interest in HIV-1 infected subjects was assessed over a period of 96 weeks in the Phase IIb trial C204 (25, 75, or 150 mg q.d.), and over a period of 48 weeks in the Phase III trials C209 and C215 (25 mg q.d.) (see Section 3.11.2).

1.14.3 Effect of TMC278 on QTcF Interval

The effect of TMC278 on the QTcF interval was initially evaluated in a thorough QT/QTc trial (C131) in healthy subjects, with TMC278 at doses of 75 mg and 300 mg q.d. The effect of TMC278 on the QTcF interval at the recommended dose of 25 mg q.d. was first assessed in a pilot trial (C151) in healthy subjects and later in a thorough QT/QTc trial that also evaluated the effect of efavirenz (EFV) 600 mg q.d. in the same setting (C152).

The effect of TMC278 on QTcF interval was also evaluated in HIV-1 infected subjects, in the Phase IIb trial and in the Phase III trials.

Further information is available from pharmacokinetic/pharmacodynamic modeling and simulation of the effect of TMC278 on the QTcF interval prolongation based on pooled data from the thorough QT/QTc trials C131 and C152.

The effect of TMC278 on QTcF interval and the relationship between TMC278 plasma concentration and QTcF interval change is discussed in Section 3.11.3.

2 SUMMARY OF RESULTS OF INDIVIDUAL TRIALS

2.1 HUMAN BIOMATERIAL STUDIES

An overview of the nonclinical, human biomaterial studies that provide supporting information on the clinical pharmacology of TMC278 is shown in Table 1. For further information on nonclinical pharmacokinetics studies, please refer to Module 2.6.4.

2.1.1 In Vitro Transport Characteristics: Study NC104

Human Caco-2 cells were used as an in vitro model to investigate the bi-directional transepithelial transport characteristics of ^{14}C-TMC278. In addition, possible inhibition of human P-gp by TMC278 was studied.

Comparison of the transepithelial permeation rates of TMC278 with those obtained for the reference compounds alniditan, levocabastine, and theophylline indicated that TMC278 has intermediate permeability. Transepithelial transport rates of TMC278 across Caco-2 monolayers were similar for initial TMC278 concentrations between 3 and 300 µM (1099 and 109926 ng/mL). TMC278 permeation across Caco-2 monolayers was polarized at early time points with efflux ratio (secretory/absorptive permeation) values of not more than 2. In addition, co-incubation with verapamil did not affect steady-state permeation rates of TMC278. These results indicate that no active transport mechanism(s), including P-gp, appear to play a role in TMC278 transepithelial permeation. Hence, TMC278 permeation is thought to occur predominantly via passive transcellular diffusion. Further, TMC278, although no substrate of P-gp, inhibits the P-gp mediated transport of paclitaxel in Caco-2 cells with an apparent 50% inhibitory concentration (IC_{50}) value of 9.2 µM (3371 ng/mL).

It is concluded that TMC278 exhibits sufficient membrane permeability to obtain adequate intestinal absorption as long as solubility and dissolution rate are not limiting at the therapeutic dose used in man. Inhibition of transepithelial permeation of P-gp substrates by TMC278 cannot be excluded. An in vivo effect of TMC278 at the intestinal absorption level is unlikely, given the low therapeutic dose of TMC278 (25 mg q.d.) and the fact that the in vivo TMC278 total plasma concentrations at this dose are more than 10-fold lower (see Section 2.6.2) than the IC_{50} value of 3371 ng/mL.

Further details on the results of this study are available in Module 4.2.2.2/TMC278-NC104.

2.1.2 Protein Binding: Study NC112

The plasma protein binding, as evaluated by equilibrium dialysis of plasma samples from healthy men after fortification with ^{3}H-labelled TMC278, was independent of the TMC278 concentration within the concentration range tested (10 to 3000 ng/mL [0.03 to 8.19 µM]), and was on average 99.7% (Table 5). The results of incubations with purified human proteins at physiological concentrations indicated that TMC278 was extensively bound to human albumin and to a lesser extent to α_1-acid glycoprotein. The blood to plasma concentration ratios were 0.67 and 0.66 at TMC278 concentrations of 100 and 1000 ng/mL [0.27 and 2.73 µM], respectively. In addition, irrespective of the concentration tested, only a very limited fraction of TMC278 was distributed to the plasma water compartment (0.003). The fraction of TMC278 distributed to plasma proteins was 0.773, and the fraction distributed to blood cells was 0.224.

In conclusion, TMC278 was extensively bound to plasma proteins, mainly to albumin, and the plasma protein binding was concentration-independent across the range of 10 to 3000 ng/mL (0.03 to 8.19 µM).

Table 5: Mean Plasma Protein Binding at Different Concentrations of TMC278 in Plasma of Healthy Men (Study NC112)

Test Concentration (ng/mL)	Protein Bound (%, ± SD)
10	99.66 ± 0.00
100	99.64 ± 0.01
300	99.62 ± 0.02
1000	99.67 ± 0.02
3000	99.70 ± 0.02

SD = standard deviation.
Source: Module 4.2.2.3/TMC278-NC112/Table 5-1

Further details on the results of this study are available in Module 4.2.2.3/TMC278-NC112.

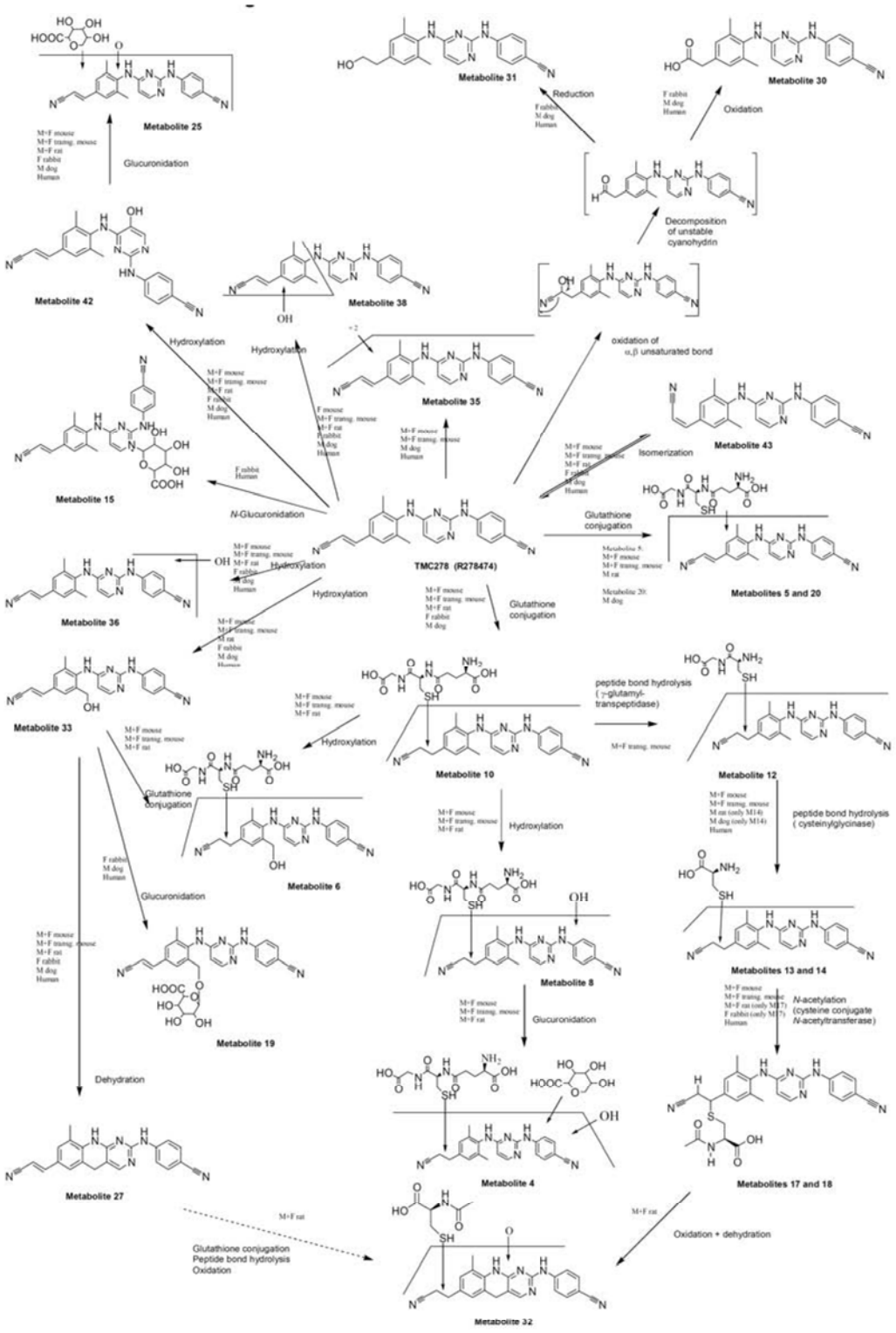
2.1.3 In Vitro and in Vivo Metabolism and Potential for Interactions

2.1.3.1 Study NC102: In Vitro Metabolism of ^{14}C-TMC278 in Hepatocytes and Liver Subcellular Fractions

The identification of the in-vitro metabolites of ^{14}C-TMC278 was done in human hepatocytes (suspensions and primary cultures) and liver subcellular fractions (microsomes and 12000 × g supernatant fractions) of humans and various animal species. TMC278 (5 µM [1832 ng/mL]) was incubated in the above matrices at 37°C for various time periods, and incubates were analyzed by radio-high-performance liquid chromatography (HPLC). Co-chromatography, enzyme hydrolysis, liquid chromatography with tandem mass-spectrometry (LC-MS/MS) and nuclear magnetic resonance (NMR) techniques were used for the identification of metabolites.

TMC278 was metabolized via different metabolic pathways, including aromatic and aliphatic hydroxylation, glutathione conjugation, *N*-glucuronidation, nitrile release, followed by reduction/oxidation, and isomerization (Figure 1). Aromatic hydroxylation at the pyrimidinyl moiety subsequently followed by glucuronidation was the metabolic pathway representing the main in vitro biotransformation. Aliphatic hydroxylation at one of the methyl groups of the cyanoethenyl-2,6-dimethylphenyl moiety, subsequently followed by dehydration to form a tricyclic metabolite, proved to be another important metabolic pathway. Aliphatic hydroxylation in combination with glucuronidation was also observed. The mercapturic acid biosynthesis route proved to be a minor pathway, and not all intermediary metabolites were detected. The release of the nitrile group followed by reduction/oxidation, resulting in the formation of an alcohol metabolite and a carboxylic acid metabolite, was another minor metabolic pathway. *N*-glucuronidation at the pyrimidinyl moiety of TMC278 was also detected.

All identified metabolites detected in human matrices were also detected in at least one animal species, thus, there are no specific human metabolites.



Source: Module 4.2.2.4/TMC278-NC102/Figure 5-11

Figure 1: In Vitro Metabolic Pathways of TMC278 in Mice, Rats, Rabbits, Dogs, and Humans (Study NC102)

Further details on the results of this study are available in Module 4.2.2.4/TMC278-NC102.

2.1.3.2 STUDY NC157 (C119): IN VIVO METABOLISM OF ^{14}C-TMC278 IN HUMAN URINE, FECES, AND PLASMA

The metabolites of ^{14}C-TMC278 were determined in feces, urine, and plasma collected from healthy male subjects after a single oral dose of 150 mg ^{14}C-TMC278 (polyethylene glycol [PEG] 400-based solution) in trial C119 (see Section 2.2). Feces extracts, pooled and concentrated urine of individual subjects, and overall pooled plasma samples were analyzed by radio-HPLC. Co-chromatography with authentic substances, enzyme hydrolysis, and LC-MS/MS techniques were used for the identification of metabolites.

The radioactivity was mainly excreted in feces (85.1% of the dose) and to a lesser extent in urine (6.1%) (refer to Module 4.2.2.4/TMC278-NC157/Table 6-2). The total excretion after 2 weeks amounted to a mean of 91.2% of the dose. Unchanged TMC278 accounted for a mean of 25.5% of the dose in feces.

TMC278 was extensively metabolized, with more than 15 metabolites detected. The most abundant metabolite originated from oxidation at the 5-position of the pyrimidinyl moiety (metabolite 42), and accounted for a mean of 16.1% of the TMC278-related radioactivity in feces (Table 6). Three other metabolites (metabolites 30, 33, and 35) each accounted on average for 2.2% to 3.0% of the dose. Metabolite 30 was a carboxylic acid metabolite on the cyanoethenyl moiety, metabolite 33 resulted from methyl hydroxylation at the dimethylphenyl moiety, and the identity of metabolite 35 was unknown. Further dehydration of hydroxymethyl TMC278 resulted in a tricyclic metabolite (metabolite 27, 0.6%), which was further oxidized (metabolite 23, 0.7%) or transformed to a carboxylic acid metabolite (metabolite 11, 1.6%).

The in vitro antiviral activities of TMC278 metabolites 33 and 42 were tested on wildtype and mutant HIV-1 strains. The 50% effective concentration in cell-based assays (EC_{50}) for wildtype virus of metabolite 33 (0.4 nM) was comparable to the EC_{50} of TMC278 while it was 36-fold higher (less active) for metabolite 42 (18 nM) (refer to Module 5.3.3.1/TMC278-C119-CRR/Section 4.2.9.2). Metabolites 33 and 42 both lost activity on the resistant virus strains tested.

In urine, apart from the carboxylic acid metabolite (metabolite 30, 0.03% of the dose in urine), the other metabolites were phase-2 metabolites (glucuronides or glutathione-derived conjugates). Overall, glutathione-derived metabolites accounted for a mean of 1.2% of the dose in urine.

Unchanged drug accounted for the major part of the total radioactivity in plasma (76% based on C_{max}, 51% based on the area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration [AUC_{last}]). Several minor metabolites were detected in plasma, namely the glucuronide of TMC278 (metabolite 15, $\leq$ 10.2% of the sample radioactivity), the tricyclic metabolite (metabolite 27, $\leq$ 9.7% of the sample radioactivity) and hydroxymethyl TMC278 (metabolite 33, $\leq$ 5.1% of the sample radioactivity) (refer to Module 5.3.3.1/TMC278-NC157/Table 6-6); others (glucuronide of hydroxymethyl TMC278 and of hydroxylated TMC278) were only traceable by LC-MS/MS (Figure 2).

Table 6: Excretion of TMC278 and its Metabolites in Feces After a Single Oral Dose of 150 mg ^{14}C-TMC278 in Healthy Men (Study NC157; Trial C119)

Metabolite	Identity	Mean (± SD) % of Dose (N = 6)
3	Unknown	0.3 ± .3
11	Carboxylic acid metabolite of metabolite 27	1.6 ± 0.5
23	Oxidized metabolite of metabolite 27	0.7 ± 0.9
27	Tricyclic metabolite, originating from oxidation and dehydration most probably of metabolite 33	0.6 ± 0.4
30	Carboxylic acid metabolite on the cyanoethenyl moiety	2.7 ± 1.1
33	Hydroxymethyl TMC278	3.0 ± 0.8
35	Unknown	2.2 ± 0.9
39	cis 5-hydroxy pyrimidinyl TMC278 (cis isomer of metabolite 42)	0.4 ± 0.3
42	Hydroxyl metabolite at the 5-position of the pyrimidinyl moiety of TMC278	16.1 ± 4.0
43	cis TMC278	0.6 ± 0.5
UD	TMC278	25.5 ± 9.3
46	Unknown, most probably originating from a glutathione-derived metabolite on the cyanoethenyl moiety	0.5 ± 0.6
Sum		**54.0 ± 5.1**

N = maximum number of subjects with data; UD = unchanged drug.
Source: Module 4.2.2.4/TMC278-NC157/Table 6-5