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RESEARCH**

APPLICATION NUMBER:

209471Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209471
Link to EDR	\\CDSESUB1\evsprod\NDA209471\0036
Submission Date	7/27/2021; PDUFA date: 1/27/2022
Submission Type	Resubmission; 505(b)(2) to Ultracet (acetaminophen 325 mg/tramadol HCl 37.5 mg (NDA 21123) and Motrin (ibuprofen tablet) (NDA 17463))
Brand Name	Combogesic tablets
Generic Name	-
Dosage Form and Strength	Oral tablet with acetaminophen 325 mg and ibuprofen 97.5 mg
Route of Administration	Oral
Proposed Indication	Short term management of mild to moderate acute pain
Dosage Regimen	The recommended adult dose of Combogesic is 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.
Applicant	AFT Pharmaceuticals
Associated IND	IND 107435
OCP Reviewer	Wei Qiu, Ph.D.
OCP Team leader	Yun Xu, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information submitted in the current application, NDA 209471 resubmission, for Combogesic tablet, submitted on 7/27/2021. From a clinical pharmacology perspective, the information submitted in the NDA resubmission is acceptable.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Bioequivalence between the reformulated Combogesic tablets within this resubmission and the original formulation Combogesic tablets included in the original NDA submission was demonstrated under both fasting and high-fat fed conditions in two bioequivalence studies (ACIB-T0218-16 under fasting condition and ACIB-T0218-17 under high-fat fed condition). The 90% confidence intervals (90% CI) for geometric mean ratios of C _{max} , AUC _{0-t} , and AUC _{0-inf} for both acetaminophen and ibuprofen between these two formulation Combogesic tablets fell within the 80-125% bioequivalence limits under both fasting and fed states.
General dosing instructions	3 tablets Q6H as needed for pain relief, up to a maximum of 12 tablets per day.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Not recommended in patients with renal impairment. Not recommended in patients with hepatic impairment
Labeling	Edits are made on presentation of PK data in section 12.3 of the proposed labeling. See Section 2.4 of this review for more details.
Bridge between the to-be-marketed and clinical trial formulations	The reformulated final to-be-marketed formulation and the original clinical trial formulation were used in the bioequivalence studies (ACIB-T0218-16 under fasting condition and ACIB-T0218-17 under high-fat fed condition) where bioequivalence between these two formulations was demonstrated.
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The Applicant conducted two bioequivalence studies (ACIB-T0218-16 under fasting condition and ACIB-T0218-17 under high-fat fed condition) and demonstrated bioequivalence between the reformulated Combogesic tablets and the original formulation Combogesic tablets under both fasting and high-fat fed conditions. The 90% confidence intervals (90% CI) for geometric mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} for both acetaminophen and ibuprofen between these two formulation Combogesic tablets fell within the 80-125% bioequivalence limits under both fasting and fed states.

- **Regulatory History**

The clinical pharmacology review for the original NDA submission can be found in DARRTS documented on November 20, 2017. The submission was acceptable from clinical pharmacology perspective. In the Complete Response (CR) letter issued on November 06, 2020 to NDA 209471, the only deficiency with the NDA application was related to facility inspections. It was stated “An inspection of the (b) (4) facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with cGMP”.

In this NDA 209471 resubmission, the Applicant replaced their original formulation Combogesic tablet, aka “standard Combogesic tablet” manufactured by (b) (4) with a reformulated Combogesic tablet manufactured by Mayne Pharma Inc., Greenville, NC, USA. To support the reformulated Combogesic tablet, in the Type C meeting package submitted in 2019, the sponsor stated that they conducted two bioequivalence studies demonstrating that the reformulated Combogesic tablets were bioequivalent to the original formulation of Combogesic under fasting and fed conditions. The comments conveyed to the sponsor at that time was that food effect on reformulated Combogesic tablet needs to be assessed under high fat fed condition as described in the food effect guidance. In this resubmission, the Applicant submitted two bioequivalence studies ACIB-T0218-16 and ACIB-T0218-17 comparing the reformulated Combogesic tablets included within this resubmission with the original formulation Combogesic tablets included in their original submission under fasting and high-fat fed conditions. This review will focus on the two bioequivalence studies.

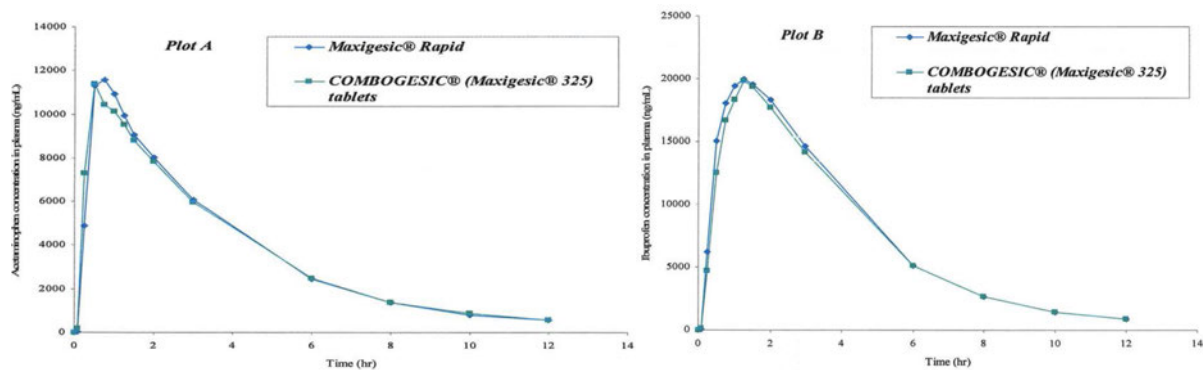
- **Summary of Pharmacokinetic Results**

Bioequivalence of Reformulated Combogesic Tablets and Original Formulation Combogesic Tablets under Fasting Condition (Results from ACIB-T0218-16)

Study ACIB-T0218-16 was a randomized, single-dose, 2-way crossover, open label study to evaluate and compare acetaminophen and ibuprofen PK parameters of three reformulated Combogesic tablets and three original formulation Combogesic tablets in 30 healthy volunteers under fasting condition. In this study, reformulated Combogesic tablet was also known as Maxigesic Rapid and the original formulation of Combogesic tablet was also known as Maxigesic 325 tablet. There was a washout period of at least 3 days between study periods. Blood samples for the determination of acetaminophen and ibuprofen concentrations in plasma were collected at the following time points: pre-dose and at 5, 15, 30, and 45 min, 1.0, 1.25, 1.5, 2.0, 3.0, 6.0, 8.0, 10.0 and 12.0 hours after study drug administration in each study period.

The mean acetaminophen and ibuprofen plasma concentration-time profiles are shown in **Figure 1**. The PK results and statistical analysis results for bioequivalence assessment of acetaminophen and ibuprofen PK parameters including C_{max}, AUC_{0-t}, and AUC_{0-inf} for reformulated Combogesic tablets and original formulation Combogesic tablets are presented in **Tables 1** and **2**. Median (min, max) T_{max} values for acetaminophen were similar: 0.75 (0.25, 2.00) h for reformulation and 0.50 (0.25, 2.00) h for original formulation. Median (min, max) T_{max} values for ibuprofen were similar: 1.25 (0.25, 3.00) h for reformulation and 1.25 (0.50, 6.00) h for original formulation. Acetaminophen and ibuprofen C_{max}, AUC_{0-t}, and AUC_{0-inf} values following a single dose administration of three reformulated Combogesic tablets are bioequivalent to that for a single dose administration of three original formulation Combogesic tablets under fasting condition because the 90% CIs of the geometric mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} for both acetaminophen and ibuprofen fell within the 80-125% bioequivalence limits under fasting condition. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for acetaminophen C_{max}, AUC_{0-t}, and AUC_{0-inf} were 99.37% (87.89 – 112.34%), 101.19 (98.51 – 103.95%), and 101.17% (98.38 – 104.04%), respectively. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for ibuprofen C_{max}, AUC_{0-t}, and AUC_{0-inf} were 112.34% (101.82 – 123.95%), 104.28 (100.98 – 107.70%), and 104.33% (101.25 – 107.51%), respectively.

Figure 1 Mean Acetaminophen (Plot A) and Ibuprofen (Plot B) Plasma Concentration-Time Profiles Following Single Dose Administrations of 3 x Reformulated Combogesic Tablets (aka Maxigesic Rapid) and 3 x Original Formulation Combogesic Tablets under Fasting Condition (Study ACIB-T0218-16)



Note: In Study ACIB-T0218-16, reformulated Combogesic tablet is also known as Maxigesic Rapid; Original formulation Combogesic tablet is also known as Maxigesic 325 tablet

Source: Study ACIB-T0218-16 Report Synopsis

Table 1 Mean ($\pm$ SD) Pharmacokinetic Parameters of Acetaminophen and Ibuprofen following Single Dose Administrations of 3 x Reformulated Combogesic Tablets and 3 x Original Formulation Combogesic Tablets in the Fasted State (Study ACIB-T0218-16)

Acetaminophen		
Pharmacokinetic Parameter	REFORMULATED COMBOGESIC® (N=29)	ORIGINAL FORMULATION COMBOGESIC® (N=29)
C_{max} (ng/ml)	<i>14877.280 $\pm$ 5969.64</i>	<i>15336.425 $\pm$ 6687.11</i>
AUC_{0→t} (ng.h/ml)	<i>44637.6 $\pm$ 11784.46</i>	<i>44365.5 $\pm$ 12615.10</i>
AUC_{0→∞} (ng.h/ml)	<i>47437.2 $\pm$ 13053.06</i>	<i>47240.7 $\pm$ 14414.20</i>
t_{max} (h) *	<i>0.75 (0.25-2.00)</i>	<i>0.50 (0.25-2.00)</i>
K_{el} (1/h)	<i>0.2233 $\pm$ 0.05</i>	<i>0.2232 $\pm$ 0.05</i>
Ibuprofen		
Pharmacokinetic Parameter	REFORMULATED COMBOGESIC® (N=30)	ORIGINAL FORMULATION COMBOGESIC® (N=30)
C_{max} (ng/ml)	<i>25579.823 $\pm$ 5996.24</i>	<i>22852.777 $\pm$ 5146.03</i>
AUC_{0→t} (ng.h/ml)	<i>91888.7 $\pm$ 24015.73</i>	<i>88754.1 $\pm$ 25476.98</i>
AUC_{0→∞} (ng.h/ml)	<i>95621.9 $\pm$ 28252.68</i>	<i>92258.7 $\pm$ 29320.30</i>
t_{max} (h) *	<i>1.25 (0.25-3.00)</i>	<i>1.25 (0.50-6.00)</i>
K_{el} (1/h)	<i>0.3076 $\pm$ 0.06</i>	<i>0.3111 $\pm$ 0.06</i>

*t_{max}: median (min, max); n = 29 for acetaminophen PK (after excluding subject no. 19 who has a pre-dose concentration > 5% of C_{max})
Source: Section 2.7.2 Summary of Clinical Pharmacology Studies Table 13

Table 2 Bioequivalence Analysis of Acetaminophen and Ibuprofen PK for the Reformulated Combogesic Tablets and the Original Formulation Combogesic Tablets in the Fasted State (Study ACIB-T0218-16)

Acetaminophen			
Pharmacokinetic Parameter	90% Confidence interval		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	<i>99.37</i>	<i>87.89</i>	<i>112.34</i>
AUC_{0→t}	<i>101.19</i>	<i>98.51</i>	<i>103.95</i>
AUC_{0→∞}	<i>101.17</i>	<i>98.38</i>	<i>104.04</i>
Ibuprofen			
Pharmacokinetic Parameter	90% Confidence interval		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	<i>112.34</i>	<i>101.82</i>	<i>123.95</i>
AUC_{0→t}	<i>104.28</i>	<i>100.98</i>	<i>107.70</i>
AUC_{0→∞}	<i>104.33</i>	<i>101.25</i>	<i>107.51</i>

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies Table 14

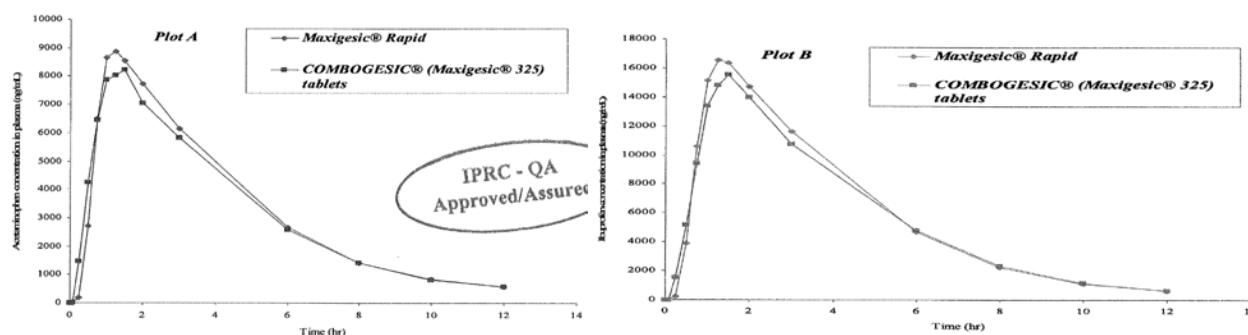
Bioequivalence of Reformulated Combogesic Tablets and Original Formulation Combogesic Tablets under Fed Condition (Results from Study ACIB-T0218-17)

Study ACIB-T0218-17 was a randomized, single-dose, 2-way crossover, open label study to evaluate and compare acetaminophen and ibuprofen PK parameters of three reformulated Combogesic tablets and three original formulation Combogesic tablets in 30 healthy volunteers under high fat fed condition. In study Day 1 of each study period, subjects received a standardized breakfast served 30 minutes prior to the study drug administration. The standardized breakfast supplied around 927 kcal, about 50% of which are fat calories. In this study, reformulated Combogesic tablet was also known as Maxigesic Rapid and the original formulation Combogesic tablet is also known as Maxigesic 325 tablet. There was a washout period of at least 3 days between study periods. Blood samples for the determination of acetaminophen and ibuprofen concentrations in plasma were collected at the following times: pre-dose, and at 5, 15, 30, and 45 min, 1.0, 1.25, 1.5, 2.0, 3.0, 6.0, 8.0, 10.0 and 12.0 hours after study drug administration in each study period.

The mean acetaminophen and ibuprofen plasma concentration-time profiles are shown in **Figure 2**. The PK results and statistical analysis results for bioequivalence assessment of acetaminophen

and ibuprofen PK parameters including C_{max}, AUC_{0-t}, and AUC_{0-inf} for reformulated Combogesic tablets and original formulation Combogesic tablets are presented in **Tables 3** and **4**. Median (min, max) T_{max} values for acetaminophen were similar: 1.25 (0.5, 6.00) h for the reformulation and 1.25 (0.5, 3.00) h for original formulation. Median (min, max) T_{max} values for ibuprofen were similar: 1.25 (0.75, 6.00) h for reformulation and 1.38 (0.75, 6.00) h for original formulation. Acetaminophen and ibuprofen C_{max}, AUC_{0-t}, and AUC_{0-inf} values following a single dose administration of three reformulated Combogesic tablets are bioequivalent to that for a single dose administration of three original formulation Combogesic tablets under high-fat fed condition because the 90% CIs of the geometric mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} for both acetaminophen and ibuprofen fell within the 80-125% bioequivalence limits under high-fat fed condition. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for acetaminophen C_{max}, AUC_{0-t}, and AUC_{0-inf} were 107.63% (101.17 – 114.50%), 103.11 (100.01 – 106.31%), and 103.07% (100.17 – 106.06%), respectively. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for ibuprofen C_{max}, AUC_{0-t}, and AUC_{0-inf} were 113.14% (106.23 – 120.49%), 103.32 (99.79 – 106.98%), and 103.31% (99.89 – 106.84%), respectively.

Figure 2 Mean Acetaminophen (Plot A) and Ibuprofen (Plot B) Plasma Concentration-Time Profiles Following Single Dose Administrations of 3 x Reformulated Combogesic Tablets (aka Maxigesic Rapid) and 3 x Original Formulation Combogesic Tablets under High-fat Fed Condition (Study ACIB-T0218-17)



Note: in Study ACIB-T0218-17, reformulated Combogesic tablet is also known as Maxigesic Rapid; Original formulation Combogesic tablet is also known as Maxigesic 325 tablet

Source: Study ACIB-T0218-17 Report Synopsis

Table 3 Mean ($\pm$ SD) Pharmacokinetic Parameters of Acetaminophen and Ibuprofen following Single Dose Administrations of 3 x Reformulated Combogesic Tablets and 3 x Original Formulation Combogesic Tablets in the Fed State (Study ACIB-T0218-17)

Acetaminophen		
Pharmacokinetic Parameter	REFORMULATED COMBOGESIC® (N=30)	ORIGINAL FORMULATION COMBOGESIC® (N=30)
C_{max} (ng/ml)	<i>11214.182 $\pm$ 4084.46</i>	<i>10401.033 $\pm$ 3616.36</i>
AUC_{0→t} (ng.h/ml)	<i>39826.6 $\pm$ 11211.91</i>	<i>38464.1 $\pm$ 10358.65</i>
AUC_{0→∞} (ng.h/ml)	<i>42381.0 $\pm$ 12086.45</i>	<i>40986.5 $\pm$ 11332.85</i>
t_{max} (h) *	<i>1.25 (0.50-6.00)</i>	<i>1.25 (0.50-3.00)</i>
K_{el} (1/h)	<i>0.2303 $\pm$ 0.03</i>	<i>0.2415 $\pm$ 0.04</i>
Ibuprofen		
Pharmacokinetic Parameter	REFORMULATED COMBOGESIC® (N=30)	ORIGINAL FORMULATION COMBOGESIC® (N=30)
C_{max} (ng/ml)	<i>20834.673 $\pm$ 5506.39</i>	<i>18490.205 $\pm$ 5036.86</i>
AUC_{0→t} (ng.h/ml)	<i>71286.1 $\pm$ 16546.13</i>	<i>68526.4 $\pm$ 13809.82</i>
AUC_{0→∞} (ng.h/ml)	<i>73449.6 $\pm$ 17660.44</i>	<i>70598.4 $\pm$ 14821.35</i>
t_{max} (h) *	<i>1.25 (0.75 -6.00)</i>	<i>1.38 (0.75 -6.00)</i>
K_{el} (1/h)	<i>0.3222 $\pm$ 0.05</i>	<i>0.3328 $\pm$ 0.04</i>

*t_{max}: median (min, max)

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies Table 15

Table 4 Bioequivalence Analysis of Acetaminophen and Ibuprofen PK for the Reformulated Combogesic Tablets and the Original Formulation Combogesic Tablets in the Fed State (Study ACIB-T0218-17)

Acetaminophen			
Pharmacokinetic Parameter	90% Confidence interval		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	107.63	101.17	114.50
$AUC_{0 \rightarrow t}$	103.11	100.01	106.31
$AUC_{0 \rightarrow \infty}$	103.07	100.17	106.06
Ibuprofen			
Pharmacokinetic Parameter	90% Confidence interval		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	113.14	106.23	120.49
$AUC_{0 \rightarrow t}$	103.32	99.79	106.98
$AUC_{0 \rightarrow \infty}$	103.31	99.89	106.84

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies Table 16.

- **Office of Study Integrity and Surveillance (OSIS) Inspection**

Based on OSIS memo in DARRTS dated October 04, 2021, OSIS declined to conduct on-site inspection on clinical site and analytical site (b) (4) for studies ACIB-T0218-16 and ACIB-T0218-17. It was concluded that inspections are not warranted because the Office of Regulatory Affairs (ORA) inspected the clinical site in October 2018, which falls within the surveillance interval. OSIS inspected the analytical site in (b) (4), which falls within the surveillance interval. The final classification for both inspections was No Action Indicated (NAI).

2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication?

Combogesic is a combination of acetaminophen, an analgesic and antipyretic, and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), and is indicated for the short-term management of mild to moderate acute pain.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

As of today (12/20/2021), labeling negotiation is still ongoing. Tentative labeling recommendations are shown below: recommended deletions are shown as red ~~strikethrough~~ and additions are shown as blue underlined text:



3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical LC/MS/MS methods for the determination of acetaminophen and ibuprofen concentrations in human plasma were adequately validated. The assay precision and accuracy of the analytical methods used in Study ACIB-T0218-16 and ACIB-T0218-17 are summarized in **Table 5**.

Table 5 Summary of Bioanalytical Assays for Acetaminophen and Ibuprofen Concentrations in Plasma (Study ACIB-T0218-16 and Study ACIB-T0218-17)

	Study ACIB-T0218-16		Study ACIB-T0218-17	
	Acetaminophen	Ibuprofen	Acetaminophen	Ibuprofen
Method validation	Method validation report ACE-0114-ORG	Method validation report IBU-0114-B	Method validation report ACE-0114-ORG	Method validation report IBU-0114-B
Nominal range for the calibration curve	50.000 – 20000.000 ng/mL	50.000 – 35000.000 ng/mL	50.000 – 20000.000 ng/mL	50.000 – 35000.000 ng/mL
LLOQ	50.000 ng/mL	50.000 ng/mL	50.000 ng/mL	50.000 ng/mL
QC	150.000, 2500.000, 10000.000, and 15000.000 ng/mL	150.000, 1250.000, 12500.000, 17500.000, and 27000.000 ng/mL	150.000, 2500.000, 10000.000, and 15000.000 ng/mL	150.000, 1250.000, 12500.000, 17500.000, and 27000.000 ng/mL
Precision (%CV)	3.67 to 5.18%	4.35 to 7.94%	2.12 to 6.00%	4.17 – 11.01%
Accuracy (% difference from theoretical)	-1.82 to 1.28%	-1.68 to 6.12%	-2.99 to 5.11%	-2.19 – 7.36%

Source: 1. ACIB-T0218-16 Study Report Appendix 16.1.8 Bioanalytical Information 2. ACIB-T0218-17 Study Report Appendix 16.1.8 Bioanalytical Information

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CLINICAL PHARMACOLOGY REVIEW

NDA: 209-471	Submission Date(s): March 1, 2017; April 11, 2017; July 24, 2017; July 26, 2017
Brand Name	Combogesic
Generic Name	Acetaminophen 325 mg/ibuprofen 97.5 mg tablet
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	AFT Pharmaceuticals
Relevant IND	IND 107,435
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Oral tablet; Acetaminophen 325 mg/ibuprofen 97.5 mg
Indication	Short term management of mild to moderate acute pain
Proposed Dosing Regimen	3 tablets Q6H as needed for pain relief, up to a maximum of 12 tablets per day

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this NDA submission dated March 1, 2017; April 11, 2017; July 24, 2017; July 26, 2017, and finds it acceptable. This product will not be approved during this review cycle and there is no labeling recommendation or negotiation in this review cycle.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical pharmacology study supported the dosing regimen used in the clinical trials.
General dosing instructions	3 tablets Q6H as needed for pain relief, up to a maximum of 12 tablets per day
Dosing in patient subgroups (intrinsic and extrinsic factors)	Not recommended in patients with renal impairment. Not recommended in patients with hepatic impairment
Labeling	This product will not be approved during this review cycle and there is no labeling recommendation at this time.
Bridge between the to-be-marketed and clinical trial formulations	The FDC 325/97.5 tablets used in all clinical studies have the same formulation as the proposed to-be-marketed product.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

AFT Pharmaceuticals submitted an original 505(b)(2) NDA 209-471 on March 1, 2017 for a fixed dose combination, Combogesic (acetaminophen 325 mg/ibuprofen 97.5 mg tablet) (aka FDC 325/97.5 tablet) for the short-term management of mild to moderate acute pain. The proposed dosing regimen is to administer 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.

The sponsor conducted 1 pivotal efficacy/safety study (Phase 3 Study AFT-MX-6) with FDC 325/97.5 tablet. In addition, the sponsor proposed to use the efficacy/safety data with a higher strength of fixed dose combination of acetaminophen and ibuprofen (aka FDC 500/150 tablet) to support this application for FDC 325/97.5 table.

As a 505(b)(2) application, the sponsor proposed to rely in part on the agency's previous findings of efficacy and safety of their identified listed drug products, Ultracet (acetaminophen 325 mg/tramadol HCl 37.5 mg) (NDA 21-123) tablet and Motrin (ibuprofen tablet) (NDA 17-463). Because Motrin (NDA 17-463) was discontinued (not for safety or efficacy reasons) and no longer available, the sponsor used the ibuprofen product from Dr Reddys Laboratories (ANDA 75-682) as the reference product for

ibuprofen in the PK bridging studies (AFT-MX-13a and AFT-MX-13b). The sponsor stated that the efficacy/safety data for acetaminophen from Ultracet and Ibuprofen from Motrin are intended to be supportive. Food effect on FDC 325/97.5 tablet and dose proportionality of 1, 2, and 3 tablets of FDC 325/97.5 was evaluated in Study AFT-MX-10.

To justify the use of the data from FDC 500/150 tablet, the sponsor conducted two comparative bioavailability studies (Study AFT-MX-14a under fasting condition and Study AFT-MX-14b under fed condition) to compare PK between FDC 325/97.5 tablet and FDC 500/150 tablet. These studies also evaluated the bioavailability of oral suspension (160 mg acetaminophen plus 48 mg ibuprofen/5 mL) and Sachet (1000 mg acetaminophen and 300 mg ibuprofen per sachet), these formulations have the same acetaminophen to ibuprofen ratio of 3.33 as FDC 325/97.5 tablet and FDC 500/150 tablet. The drug interaction potential was evaluated in in vitro study ((b) (4) Human Enzyme Study), PK study NAPQI and AFT-MX-11 with FDC 500/150.

Comparative Bioavailability of FDC 325/97.5 Tablet in Comparison to Ultracet® and Ibuprofen Tablet from Dr Reddys Laboratories

In support of the 505(b)(2) application, pharmacokinetic comparisons were made between the FDC 325/97.5 tablet and the following Listed Drugs (LDs) under both fasting and fed states: Ultracet® (acetaminophen 325 mg + tramadol HCl 37.5 mg per tablet, 2 tablets for a full dose) and ibuprofen tablet from Dr Reddys Laboratories (ibuprofen 800 mg per tablet, 1 tablet for a full dose).

Under fasting and fed conditions, 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) showed higher acetaminophen C_{max} and AUC values in comparison to 2 x Ultracet® tablets (650 mg dose of acetaminophen), and 1 x ibuprofen tablet from Dr Reddys Laboratories (800 mg dose of ibuprofen) showed higher ibuprofen C_{max} and AUC values than 3 x FDC 325/97.5 tablets (292.5 mg dose of ibuprofen) due to the dose differences.

The dose normalized total exposures of acetaminophen (AUC_t/dose and AUC_{inf}/dose) for FDC 325/97.5 tablet and Ultracet® tablet met the bioequivalence (BE) criteria under both fasting and fed conditions. The acetaminophen C_{max}/dose for FDC 325/97.5 tablet was 29% greater under fasting condition and met the BE criteria under fed condition.

The dose normalized ibuprofen AUC_t and AUC_{inf} for FDC 325/97.5 tablet and ibuprofen tablet from Dr Reddys Laboratories met the BE criteria under both fasting and fed conditions. The ibuprofen C_{max}/dose for FDC 325/97.5 tablet was 19% greater under fasting condition and met the BE criteria under fed condition. These PK results suggest that the bioavailability of acetaminophen and ibuprofen for FDC 325/97.5 tablet are similar to Ultracet and ibuprofen tablet from Dr Reddys Laboratories, respectively.

Table 1 Mean (SD) **Acetaminophen** Pharmacokinetic Parameters for A Single Dose of 3 x FDC 325/97.5 Tablets (Treatment A) and A Single Dose of 2 x Ultracet® Tablets (Acetaminophen 325 mg/tramadol HCl 37.5 mg) (Treatment B) in Healthy Subjects Under Fasting Condition (Study AFT-MX-13a) and Fed Condition (Study AFT-MX-13b) and Statistical Analysis of Dose Normalized Cmax and AUCs

PK parameter	Study AFT-MX-13a (Fasting)		Study AFT-MX-13b (Fed)	
	3 x FDC 325/97.5 tablets (Treatment A) (N = 30)	2 x Ultracet tablets (acetaminophen 325 mg/tramadol HCl 37.5 mg) (Treatment B) (N = 30)	3 x FDC 325/97.5 tablets (Treatment A) (N = 29)	2 x Ultracet tablets (acetaminophen 325 mg/tramadol HCl 37.5 mg) (Treatment B) (N = 29)
Cmax (ng/mL)	16248 (8132)	8334 (3972)	9334 (3452)	6228 (3114)
Tmax (h)*	0.50 (0.17, 2.50)	0.50 (0.33, 2.50)	1.00 (0.33, 3.00)	1.25 (0.17, 6.00)
AUCt (ng.h/mL)	32760 (8872)	18850 (5018)	32662 (9253)	19929 (5688)
AUCinf (ng.h/mL)	34418 (9516)	19890 (5350)	34612 (10189)	21190 (6292)
T1/2 (h)	3.14 (0.57)	3.33 (0.81)	2.94 (0.54)	2.96 (0.59)
Geometric Mean Ratio(A/B) % (90% CI)				
Cmax/Dose	129.25% (113.42 – 147.30%)		103.77% (91.93 – 117.13%)	
AUCt/Dose	115.58% (111.68 – 119.62%)		109.31% (107.12 – 111.55%)	
AUCinf/Dose	114.57% (110.74 – 118.54%)		108.99% (106.89 – 111.13%)	

*median (min, max)

Source of data: Study AFT-MX-13a: Table 2 in the text, and tables 4 and 5 in section 14.0 Tables, Figures, and Graphs Referred to but not Included in the Text (dose normalized Cmax and AUCs were reported and are converted to absolute values in this table); Study AFT-MX-13b: Table 2 in the text, and tables 4 and 5 in section 14.0 Tables, Figures, and Graphs Referred to but not Included in the Text (dose normalized Cmax and AUCs were reported and are converted to absolute values in this table)

Table 2 Mean (SD) **Ibuprofen** Pharmacokinetic Parameters for A Single Dose of 3 x FDC 325/97.5 Tablets (Treatment A) and A Single Dose of 1 x 800 mg Ibuprofen (Treatment C) in Healthy Subjects Under Fasting Condition (Study AFT-MX-13a) and Fed Condition (Study AFT-MX-13b) and Statistical Analysis of Dose Normalized Cmax and AUCs

PK parameter	Study AFT-MX-13a (Fasting)		Study AFT-MX-13b (Fed)	
	3 x FDC 325/97.5 tablets (Treatment A) (N = 30)	1 x 800 mg Ibuprofen tablet (Treatment C) (N = 30)	3 x FDC 325/97.5 tablets (Treatment A) (N = 29)	1 x 800 mg Ibuprofen tablet (Treatment C) (N = 29)
Cmax (ng/mL)	19943 (5827)	45278 (9744)	16086 (3840)	43574 (14040)
Tmax (h)*	1.00 (0.33, 4.00)	1.00 (0.50, 4.00)	1.25 (0.50, 4.00)	1.25 (0.50, 6.00)
AUCt (ng.h/mL)	64672 (23026)	152720 (48064)	62074 (12964)	148896 (33744)
AUCinf (ng.h/mL)	66280 (24278)	156480 (50872)	64446 (14212)	156216 (40368)
T1/2 (h)	2.22 (0.29)	2.20 (0.33)	2.24 (0.27)	2.44 (0.42)
Geometric Mean Ratio(A/C) % (90% CI)				
Cmax/Dose	118.70% (110.41 – 127.62%)		104.05% (93.91 – 115.29%)	
AUCt/Dose	115.02% (110.73 – 119.47%)		114.20% (110.44 – 118.09%)	
AUCinf/Dose	115.03% (110.81 – 119.41%)		113.33% (109.68 – 117.09%)	

*median (min, max)

Source of data: Study AFT-MX-13a: Table 4 in the text, and tables 8, and 9 in section 14.0 Tables, Figures, and Graphs Referred to but not Included in the Text (dose normalized Cmax and AUCs were reported and are converted to absolute values in this table); Study AFT-MX-13b: Table 4 in the text, and tables 8, and 9 in section 14.0 Tables, Figures, and Graphs Referred to but not Included in the Text (dose normalized Cmax and AUCs were reported and are converted to absolute values in this table)

Comparative Bioavailability of FDC 325/97.5 Tablet in Comparison to FDC 500/150 Tablet

The total exposures of acetaminophen (AUCt and AUCinf) for 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) and 2 x FDC 500/150 tablets (1000 mg dose of acetaminophen) met BE criteria under both fasting and fed conditions. Acetaminophen Cmax for 3 x FDC 325/97.5 tablets was 19% greater under fasting condition and met the BE criteria under fed condition. Ibuprofen Cmax, AUCt and AUCinf for 3 x FDC 325/97.5 tablets (292.5 mg dose of ibuprofen) and 2 x FDC 500/150 tablets (300 mg dose of ibuprofen) met BE criteria under both fasting and fed conditions. Pharmacokinetic results reasonably justify the use of data from 2 x FDC 500/150 tablet as supportive information for 3 x FDC 325/97.5 tablet.

Table 3 Mean (SD) **Acetaminophen** Pharmacokinetic Parameters for A Single Dose of 3 x FDC 325/97.5 Tablets (Treatment D) and A Single Dose of 2 x FDC 500/150 Tablets (Treatment C) in Healthy Subjects Under Fasting Condition (Study AFT-MX-14a) and Fed Condition (Study AFT-MX-14b) and Statistical Analysis of Cmax and AUCs

PK parameter	Study AFT-MX-14a (Fasting)		Study AFT-MX-14b (Fed)	
	3 x FDC 325/97.5 (Treatment D) (N = 26)	2 x FDC 500/150 (Treatment C) (N = 26)	3 x FDC 325/97.5 (Treatment D) (N = 28)	2 x FDC 500/150 (Treatment C) (N = 28)
Cmax (ng/mL)	15368 (5717)	13497 (7123)	9628 (5024)	9234 (4776)
Tmax (h)*	0.50 (0.25, 3.00)	0.63 (0.25, 3.00)	1.00 (0.25, 3.00)	1.13 (0.25, 3.00)
AUCt (ng.h/mL)	32838 (7577)	32199 (8356)	31928 (9498)	31687 (9151)
AUCinf (ng.h/mL)	34651 (8388)	33832 (9155)	33788 (10188)	33726 (9850)
T1/2 (h)	3.31 (0.75)	3.04 (0.76)	2.90 (0.41)	3.00 (0.60)
Geometric Mean Ratio(D/C) % (90% CI)				
Cmax	118.84% (102.18 - 138.23%)		103.65% (88.47 - 121.43%)	
AUCt	102.49% (99.35 - 105.73%)		100.33% (97.04 - 103.74%)	
AUCinf	102.92% (99.74 - 106.21%)		99.77% (96.63 - 103.02%)	

*median (min, max)

Source of data: Study AFT-MX-14a: Table 6 in the text, Tables 8 and 9 in 14.0 Tables, Figures, and Graphs Referred to but not Included in the Text; Study AFT-MX-14b: Table 6 in the text, Tables 8 and 9 in 14.0 Tables, Figures, and Graphs Referred to but not Included in the Text

Table 4 Mean (SD) **Ibuprofen** Pharmacokinetic Parameters for A Single Dose of 3 x FDC 325/97.5 Tablets (Treatment D) and A Single Dose of 2 x FDC 500/150 Tablets (Treatment C) in Healthy Subjects Under Fasting Condition (Study AFT-MX-14a) and Fed Condition (Study AFT-MX-14b) and Statistical Analysis of Cmax and AUCs

PK parameter	Study AFT-MX-14a (Fasting)		Study AFT-MX-14b (Fed)	
	3 x FDC 325/97.5 (Treatment D) (N = 26)	2 x FDC 500/150 (Treatment C) (N = 26)	3 x FDC 325/97.5 (Treatment D) (N = 28)	2 x FDC 500/150 (Treatment C) (N = 28)
Cmax (ng/mL)	20654 (4717)	19278 (5018)	17513 (5039)	17665 (6376)
Tmax (h)*	1.13 (0.50, 6.00)	1.38 (0.50, 6.00)	1.50 (0.50, 3.00)	1.25 (0.50, 6.00)
AUCt (ng.h/mL)	76106 (16447)	75842 (13428)	64687 (13651)	66679 (13971)
AUCinf (ng.h/mL)	78329 (17471)	78439 (14464)	66966 (14490)	68976 (14738)
T1/2 (h)	2.19 (0.33)	2.13 (0.26)	2.26 (0.50)	2.19 (0.29)
Geometric Mean Ratio(D/C) % (90% CI)				
Cmax	107.49% (96.69 - 119.49%)		101.41% (90.45 - 113.69%)	
AUCt	99.43% (94.48 - 104.64%)		97.12% (94.36 - 99.97%)	
AUCinf	98.99% (94.35 - 103.85%)		97.17% (94.31 - 100.12%)	

*median (min, max)

Source of data: Study AFT-MX-14a: Table 15 in the text, Tables 16 and 17 in 14.0 Tables, Figures, and Graphs referred to but not included in the text; Study AFT-MX-14b: Table 15 in the text, Tables 16 and 17 in 14.0 Tables, Figures, and Graphs referred to but not included in the text

Food Effect on FDC 325/97.5 Tablet

High-fat meal had no effect on acetaminophen AUCs or ibuprofen Cmax and AUCs except an approximately 30% decrease in acetaminophen Cmax. Median Tmax values for both acetaminophen and ibuprofen were slightly prolonged under fed conditions; 0.5 h (0.25, 3.00) fasting and 1.0 h (0.50, 3.00) fed for acetaminophen and 1.00 h (0.50, 12.00) fasting and 1.25 h (0.50, 3.00) fed for ibuprofen. Food is not expected to have clinical significance on PK of this product and it may be taken regardless of food.

Table 5 Mean (SD) Pharmacokinetic Parameters of Acetaminophen and Ibuprofen following the Administration of 3 x FDC 325/97.5 Tablets in Fasting (Treatment C) and Fed (Treatment D) Conditions (Study AFT-MX-10)

PK Parameter	Acetaminophen (N = 27)		Ibuprofen (N = 27)	
	3 x FDC 325/97.5 Fasting (Treatment C)	3 x FDC 325/97.5 Fed (Treatment D)	3 x FDC 325/97.5 Fasting (Treatment C)	3 x FDC 325/97.5 Fed (Treatment D)
Cmax (ng/mL)	16548 (6746)	11724 (3828)	21055 (3704)	19083 (4848)
Tmax (h)*	0.50 (0.25, 3.00)	1.00 (0.50, 3.00)	1.00 (0.50, 12.00)	1.25 (0.50, 3.00)
AUCt (ng.h/mL)	40535 (12341)	37811 (10392)	78495 (21710)	68908 (18262)
AUCinf (ng.h/mL)	42655 (13218)	40158 (11236)**	79772 (23565)**	71510 (19903)
T1/2 (h)	3.28 (1.24)	3.34 (1.20)	2.16 (0.36)	2.22 (0.38)
Geometric Mean Ratio(D/C) % (90% CI)				
Cmax	72.78 (63.00 – 84.08)		88.87 (81.17 – 97.29)	
AUCt	93.83 (89.54 – 98.31)		88.01 (84.24 – 91.93)	
AUCinf	93.84 (90.61 – 97.18)		89.88 (86.12 – 93.79)	

*n = 26; **median (min, max)

Source: Study AFT-MX-10: Tables 4 and 6 in the text and Tables 8, 9, 23, and 24 in Section 14.0 Tables, Figures, and Graphs Referred to but not Included in the text

Dose Proportionality over the Range of 1, 2, and 3 Tablets of FDC 325/97.5

Following a single dose administration of 1, 2, and 3 tablets of FDC 325/97.5 to healthy volunteers under fasting condition, acetaminophen and ibuprofen AUC values were dose proportional based on the analysis on log transformed AUC values using a power model. The slopes of log-transformed AUCt and AUCinf values for acetaminophen were 1.11, the corresponding 90% CI were 1.05 - 1.15 and 1.06 - 1.16, respectively. The slopes of log-transformed AUCt and AUCinf values for ibuprofen were 0.93 and 0.91, the corresponding 90% CI were 0.92 - 0.93 and 0.88 - 0.97, respectively. Acetaminophen and Ibuprofen Cmax values were roughly proportional with slope of 0.98 and 0.82, respectively.

Drug Interaction Potential between Acetaminophen and Ibuprofen:

No drug interaction between acetaminophen and ibuprofen has been found. In a single dose crossover study in healthy subjects, acetaminophen and ibuprofen PK for two tablets of FDC 500/150 are BE to 1000 mg acetaminophen and 300 mg ibuprofen, respectively. In another single dose crossover study in healthy subjects given acetaminophen 1000 mg and two tablets of FDC 500/150, study results showed that

ibuprofen did not alter the amount of acetaminophen undergoing oxidative metabolism, as the relative amounts of acetaminophen and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulphate-acetaminophen) excreted in urine were similar when administered alone or with the concomitant administration of ibuprofen (as a fixed combination FDC 500/150). A combination in equimolar concentrations up to 10 µM, acetaminophen and ibuprofen did not display significant inhibition of any CYP isoforms tested (CYP1A, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4).

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?

AFT Pharmaceuticals submitted an original 505(b)(2) NDA 209-471 on March 1, 2017 for a fixed dose combination Combogesic (acetaminophen 325 mg/ibuprofen 97.5 mg) (aka FDC 325/97.5) tablet for the short-term management of mild to moderate acute pain. The proposed dosing regimen is to administer 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day. The final to-be-marketed formulation was used in all clinical studies in involving FDC 325/97.5 tablets.

The sponsor has conducted 1 pivotal efficacy/safety study (Phase 3 Study AFT-MX-6) with FDC 325/97.5 tablet. In addition, the sponsor proposed to use the efficacy/safety data (Studies AFT-MX-3, AFT-MX-1 and AFT-MX-6E) with a higher strength of fixed dose combination of acetaminophen and ibuprofen (FDC 500/150 tablet) to support this application.

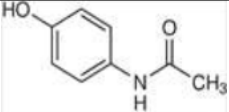
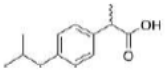
As a 505(b)(2) application, the sponsor proposed to rely in part on the agency's previous findings of efficacy and safety of their identified listed drug products, Ultracet (acetaminophen 325 mg/tramadol HCl 37.5 mg) (NDA 21-123) tablet and Motrin (NDA 17-463). In the advice letter dated 12/1/15, the sponsor was advised that "to rely on the agency's previous findings on efficacy/safety, you are recommended to identify a prescription drug product as the listed drug so all the Agency's previous findings are included in the label. If the prescription product is not available (i.e., discontinued not due to safety or effectiveness), you may use a generic product to the identified list drug in your comparative bioavailability study to establish PK bridge". Because Motrin was discontinued (not for safety or efficacy reasons) and no longer available, the sponsor performed the PK bridging study with the ibuprofen product from Dr Reddys Laboratories (ANDA 75-682). The comparative bioavailability Studies AFT-MX-13a under fasting condition and AFT-MX-13b under fed condition were conducted to establish PK bridges with Ultracet and ibuprofen tablet from Dr Reddys Laboratories. The sponsor stated that the efficacy/safety data for acetaminophen from Ultracet and Ibuprofen from Motrin are intended to be supportive. Food effect on FDC 325/97.5 tablet and dose proportionality of 1, 2, and 3 tablets of FDC 325/97.5 was evaluated in Study AFT-MX-10.

In a review team meeting held on 6/13/17, a question was raised by the clinical team regarding how is the PK comparison between the FDC 500/150 and the FDC 325/97.5. At that time, there was no direct comparison in PK between these two products. As

shown in the clinical pharmacology IR #2 included in the filing letter (dated 5/10/17), the sponsor was asked to address the PK comparison. It stated “You proposed to use pharmacokinetic data obtained from FDC 500/150 as supportive information in the NDA for FDC 325/97.5. Provide the justification how you can use these data to support FDC 325/97.5.” The sponsor did not respond the IR #2 prior to the team meeting held on 6/13/17. On 7/24/17, the sponsor responded and addressed clinical pharmacology IR #2. On 7/26/17, the sponsor submitted two additional studies AFT-MX-14a under fasting and AFT-MX14b under fed condition where a direct comparison in PK between FDC 325/97.5 and FDC 500/150 were conducted. These studies also evaluated the bioavailability of oral suspension (160 mg acetaminophen plus 48 mg ibuprofen/5 mL) and Sachet (1000 mg acetaminophen and 300 mg ibuprofen per sachet), these formulations have the same acetaminophen to ibuprofen ratio of 3.33 as FDC 325/97.5 tablet and FDC 500/150 tablet. The drug interaction potential was evaluated in in vitro study ((b) (4) Human Enzyme Study), PK study NAPQI and AFT-MX-11 with FDC 500/150.

2. *What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?*

Table 6 Physical-Chemical Properties of Acetaminophen and Ibuprofen

Drug Name	Acetaminophen	Ibuprofen
Chemical Name	N-(4-hydroxyphenyl)acetamide Hydroxyacetanilide p-Acetamidophenol N-acetyl-p-aminophenol	p- α-Methyl-4-(2-methylpropyl)-benzene acetic acid p-Isobutyl hydratropic acid 2-(4-Isobutylphenyl) propionic acid
Structure		
Molecular Formula	C ₈ H ₉ NO ₂	C ₁₃ H ₁₈ O ₂
Molecular Weight	151.16	206.28
Melting Point	168°C – 172°C	75.0°C - 78.0°C
Appearance	A white, odourless, crystalline powder with a slightly bitter taste	White to off-white fine crystalline powder with slight characteristic odour
Solubility	Soluble in boiling water and 1N sodium hydroxide, freely soluble in alcohol	Practically insoluble in water, very soluble in alcohol, in methanol, in acetone and in chloroform, slightly soluble in ethyl acetate.

All clinical studies involving FDC 325/97.5 tablet were conducted using the same formulation as that proposed for commercialization.

Table 7 Components and Composition of Acetaminophen 325 mg/Ibuprofen 97.5 mg Film-coated Tablets

S.No.	Ingredients	Qty per tablet (mg)	Function
1	Ibuprofen	97.50	Active ingredient
2	Acetaminophen	325.00	Active ingredient
3	(b) (4)		(b) (4)
4	Microcrystalline cellulose		
5	(b) (4)		
6	Croscarmellose sodium		
7	(b) (4)		
8			
9			
10			
11	Magnesium stearate		
12	Talc		
	(b) (4)		
13	(b) (4)		
14			
15			
	(b) (4)		
	(b) (4)		

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

COMBOGESIC® contains acetaminophen and ibuprofen. Acetaminophen is a non-opiate, non-salicylate analgesic. Ibuprofen possesses analgesic and anti-pyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.

COMBOGESIC® is a combination of acetaminophen, an analgesic and antipyretic, and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) and is indicated for the short-term management of mild to moderate acute pain. COMBOGESIC® is not indicated in children under 18 years of age.

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

For the short-term management of mild to moderate acute pain, the recommended adult dose of COMBOGESIC® is 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.

2.2 General Clinical Pharmacology

1. *What is known about the PK characteristics of acetaminophen for the listed drug Ultracet® (acetaminophen 325 mg/tramadol HCl 37.5 mg) Tablet (NDA 21-123) and Motrin (ibuprofen) Tablet (NDA 17-463)?*

Ultracet (acetaminophen 325 mg/tramadol HCl 37.5 mg) Tablet Labeling:

Absorption: Peak plasma concentrations of acetaminophen occur within one hour. Tmax was delayed almost one hour with food. Cmax and AUC were not affected.

Distribution: Widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~ 20%) is bound to plasma protein.

Metabolism: Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: a) conjugation with glucuronide; b) conjugation with sulfate; and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2, and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination: The half-life is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients; Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Elderly: No significant changes in PK in elderly patients with normal renal and hepatic function based on population PK analysis

Dosage and Administration: Initiate treatment with two tablets every 4 to 6 hours as needed for pain relief; maximum of 8 tablets per day; severe renal impairment, do not exceed 2 tablets every 12 hours.

Motrin (ibuprofen) Tablet Labeling:

Absorption: Rapidly absorbed with peak concentrations generally attained one to two hours after administration. Food reduced C_{max} but no appreciable decrease in AUC; the bioavailability is minimally altered by the presence of food.

With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve; above 800 mg, however, the area under the curve increases less than dose proportional. There is no evidence of drug accumulation or enzyme induction.

Metabolism: Rapidly metabolized and eliminated in the urine.

Elimination: The excretion is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours. Forty-five percent (45%) to 79% of the administered dose was recovered in the urine within 24 hours as metabolites A (25%), (+)-2-[p-(2hydroxymethyl-propyl)phenyl] propionic acid and metabolite B (37%), (+)-2-[p-(2carboxypropyl)phenyl]propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

Dosage and Administration: For mild to moderate pain, 400 mg every 4 to 6 hours as necessary for relief of pain. For rheumatoid arthritis and osteoarthritis, suggested dosage is 1200 mg – 3200 mg daily (300 mg QID; 400 mg, 600 mg or 800 mg TID or

QID). Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer MOTRIN tablets with meals or milk.

2. Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

The active moieties are acetaminophen and ibuprofen and their concentrations in plasma were measured in all PK studies.

2.3 Intrinsic Factors

1. What is the pediatric plan?

The Division agreed with the sponsor's iPSP in the communication dated 2/6/2017. The sponsor requested deferral of all assessments of safety and effectiveness of Combogesic tablet in the age-group 12 - 17 years of age and of Combogesic oral suspension (b) (4) 2 years of age and between the ages of 2 and 11 years.

2.4 Extrinsic Factors

1. Is there PK drug interaction between acetaminophen and ibuprofen?

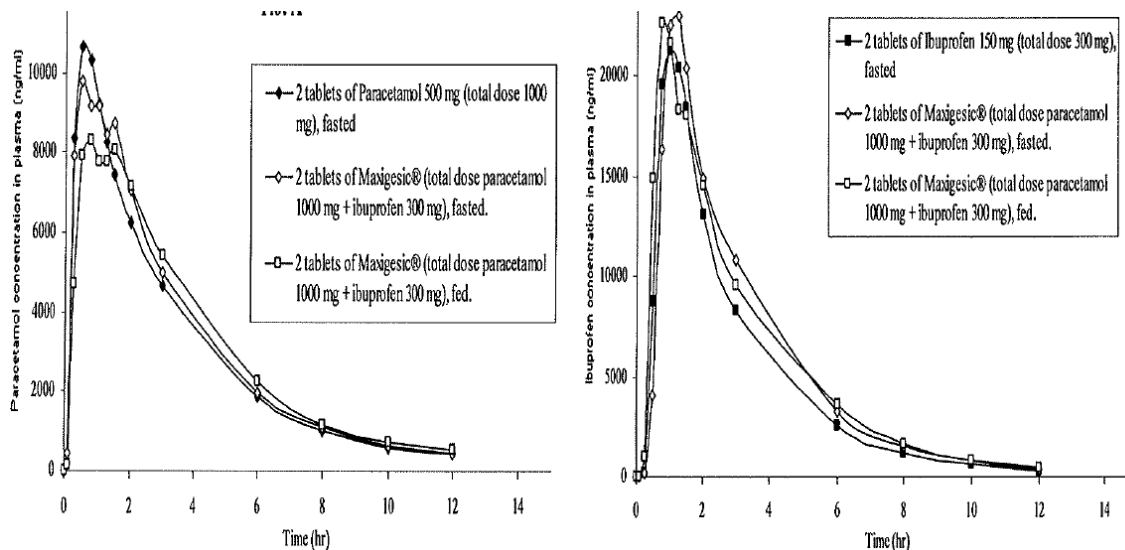
No drug interaction between acetaminophen and ibuprofen has been found. In a single dose crossover study in healthy subjects, acetaminophen and ibuprofen PK for two tablets of FDC 500/150 are bioequivalent to 1000 mg acetaminophen and 300 mg ibuprofen given alone, respectively.

The comparative bioavailability of 2 tablets of acetaminophen 500 mg fasting, 2 tablets of ibuprofen 150 mg fasting, 2 tablets of FDC 500/150 fasting, and 2 tablets of FDC 500/150 fed were determined in Study AFT-MX-11. It was a single dose, randomized, open-label, 4-way crossover study in healthy volunteers. The following treatments were administered during the studies:

- **Treatment A:** 2 x Acetaminophen 500 mg tablets (total acetaminophen dose 1000 mg), fasted
- **Treatment B:** 2 x Ibuprofen 150 mg tablets (total ibuprofen dose 300 mg), fasted
- **Treatment C:** 2 x FDC 500/150 tablets (total acetaminophen dose 1000 mg + total ibuprofen 300 mg), fasted
- **Treatment D:** 2 x FDC 500/150 tablets (total acetaminophen dose 1000 mg + total ibuprofen 300 mg), fed

Treatment periods were separated by a 7-day washout period. Blood samples for PK determination were collected from each subject at pre-dose, and at 5, 15, 30, 45 min and at 1, 1.25, 1.5, 2, 3, 6, 8, 10, and 12-hour post-dose. The mean acetaminophen and ibuprofen plasma concentration-time profiles are shown in **Figure 1**.

Figure 1 Acetaminophen (Left Panel) Mean Plasma Concentrations after A Single Dose Administration of Treatments A, C and D, Ibuprofen (Right Panel) Mean Plasma Concentrations after A Single Dose Administration of Treatments B, C and D to 26 Health Subjects (Study AFT-MX-11)



Acetaminophen and ibuprofen C_{max}, AUC_t and AUC_{inf} (**Table 8**) were similar between the fixed dose combination and mono-components. The 90% CIs for acetaminophen and ibuprofen C_{max}, AUC_t and AUC_{inf} ratios fell within the 80% to 125% range (**Tables 9** and **10**).

Table 8 Acetaminophen PK Parameters for Treatment A (2 x Acetaminophen 500 mg Tablets, Fasting), Treatment C (2 x FDC 500/150 Tablets, Fasting) and Treatment D (2 x FDC 500/150 Tablets, Fed) and Ibuprofen PK Parameters for Treatment B (2 x Ibuprofen 150 mg Tablets, Fasting), Treatment C (2 x FDC 500/150 Tablets, Fasting) and Treatment D (2 x FDC 500/150 Tablets, Fed) (Study AFT-MX-11)

	C _{max} (ng/mL)	AUC _{0→t} (ng.h/mL)	AUC _{0→∞} (ng.h/mL)	T _{max} (hrs)	T _{1/2} (hrs)
Acetaminophen					
<i>Treatment A (fast)</i>	14873.9	366508.6	38422	0.76	3.11
<i>Treatment C (fast)</i>	13894.9	38321.3	40465.5	0.73	3.14
<i>Treatment D (fed)</i>	12919.9	38111.3	40800.4	1.15	3.47
Ibuprofen					
<i>Treatment B (fast)</i>	22081.5	78563.9	80842.2	1.39	2.29
<i>Treatment C (fast)</i>	21481.8	80116.9	82298.4	1.6	2.12
<i>Treatment D (fed)</i>	20392.7	70247.6	72196.8	1.3	2.08

Table 9 Bioequivalence Analysis on Acetaminophen PK for Treatment A (2 x Acetaminophen 500 mg Tablets, Fasting) and Treatment C (2 x FDC 500/150 Tablets, Fasting)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C _{max}	104.42	88.99	122.52	33.68
AUC _{0→t}	96.28	92.84	99.84	7.66
AUC _{0→∞}	96.08	92.46	99.85	8.10

Source: Study AFT-MX-11: Table 1

Table 10 Bioequivalence Analysis on Ibuprofen PK for Treatment B (2 x Ibuprofen 150 mg Tablets, Fasting) and Treatment C (2 x FDC 500/150 Tablets, Fasting)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C _{max}	102.85	90.21	117.26	27.62
AUC _{0→t}	98.83	93.48	104.47	11.71
AUC _{0→∞}	98.94	93.98	104.16	10.83

Source: Study AFT-MX-11: Table 5

Comments: Lack of significant drug interaction between acetaminophen and ibuprofen was also supported by the results obtained from NAPQI study and some in vitro findings in human liver microsomes:

(1) In a single dose, randomized crossover study (NAPQI Study) in 12 healthy subjects given acetaminophen 1000 mg (Treatment A) and two tablets of FDC 500/150 (Treatment B) under fasting conditions, study results showed that ibuprofen did not alter the amount of acetaminophen undergoing oxidative metabolism, as the relative amounts of acetaminophen and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulphate-acetaminophen) excreted in the urine over 24 hours were similar when administered alone or with the concomitant administration of ibuprofen (as a fixed combination FDC 500/150).

Table 11 Amounts of acetaminophen and its metabolites excreted in the urine

Xut	Ratio(Test/Ref)			% of Total Excretion					
				Treatment B (Maxigesic®)			Treatment A (Panadol®)		
	Estimate	90% CI for Difference		Estimate	LL 95%	UL95%	Estimate	LL 95%	UL95%
Cysteine	110.3%	57.5%	211.5%	3.2%	1.8%	5.9%	2.8%	1.7%	4.6%
Mercapturate	102.3%	60.0%	174.4%	5.1%	3.0%	8.9%	4.8%	3.2%	7.3%
Glucuronide	96.3%	76.9%	120.5%	66.7%	62.2%	71.7%	67.6%	61.2%	74.7%
Sulfate	101.6%	78.4%	131.5%	19.6%	16.2%	23.7%	18.8%	14.5%	24.2%
Paracetamol	102.8%	75.6%	139.9%	1.9%	1.2%	2.8%	1.7%	1.2%	2.4%

LL=lower limit, UL = upper limit Test= Maxigesic®, Reference= Panadol®

(2) In human liver microsomes, a combination of 10 µM acetaminophen and 10 µM ibuprofen displayed no significant inhibition of any of the six CYP isoforms tested (CYP1A, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4).

2.5 General Biopharmaceutics

1. What is and comparative bioavailability of FDC 325/97.5 tablet vs Ultracet (NDA 21-123) and ibuprofen tablet from Dr Reddys Laboratories (ANDA 75-682)?

Under fasting and fed conditions, 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) showed higher acetaminophen C_{max} and AUC values in comparison to 2 x Ultracet® tablets (650 mg dose of acetaminophen), and ibuprofen from 1 x ibuprofen tablet from Dr Reddys Laboratories (800 mg dose of ibuprofen) showed higher ibuprofen C_{max} and AUC values than 3 x FDC 325/97.5 tablets (292.5 mg dose of ibuprofen).

Due to the dose differences in acetaminophen and ibuprofen between the FDC 325/97.5 tablet and the list drug products, comparisons were made for dose-normalized PK parameters (C_{max}/dose, AUC_t/dose and AUC_{inf}/dose). The dose normalized total exposures of acetaminophen (AUC_t/dose and AUC_{inf}/dose) for FDC 325/97.5 tablet and Ultracet® met the BE criteria under both fasting and fed conditions. Acetaminophen C_{max}/dose for FDC 325/97.5 tablet was 29% greater under fasting condition and met the BE criteria under fed condition. Ibuprofen AUC_t/dose and AUC_{inf}/dose for FDC 325/97.5 tablet and ibuprofen tablet from Dr Reddys Laboratories met the BE criteria under both fasting and fed conditions. Ibuprofen C_{max}/dose for FDC 325/97.5 tablet was 19% greater under fasting condition and met the BE criteria under fed condition.

Comparative bioavailability studies AFT-MX-13a and AFT-MX-13b had similar designs, AFT-MX-13a was conducted under fasting condition in 30 healthy subjects and AFT-MX-13b was conducted under fed condition in 30 healthy subjects. In these studies, the comparative bioavailability of a single dose of 3 x FDC 325/97.5 tablets was determined in comparison to a single dose of 2 x Ultracet tablets and 1 x 800 mg ibuprofen tablet from Dr Reddys Laboratories. Both studies were single dose, randomized, open-label, 3-period crossover study in 30 healthy volunteers. The following treatments were administered during the study:

- **Treatment A:** 3 x FDC 325/97.5 tablets (total acetaminophen dose 975 mg + total ibuprofen dose 97.5 mg)
- **Treatment B:** 2 x Ultracet tablets (total acetaminophen dose 650 mg + tramadol HCl 75 mg)
- **Treatment C:** 1 x Ibuprofen 800 mg tablet (total ibuprofen dose 800 mg)

Treatment periods were separated by a 3-day washout period. Blood samples for pharmacokinetic determination were collected from each subject at pre-dose, and at 10, 20, 30, 45 min and at 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12-hour post-dose.

The mean acetaminophen plasma concentration-time profiles are shown in **Figure 2**. Ibuprofen plasma concentration-time profiles are presented in **Figure 3**.

Figure 2 Mean Acetaminophen Plasma Concentration Versus Time for Treatment A (3 x FDC 325/97.5 tablets (total acetaminophen dose 975 mg) and Treatment B (2 x Ultracet tablets (total acetaminophen dose 650 mg)) under Fasting Condition (Left Panel) (Study AFT-MX-13a) and Fed Conditions (Right Panel) (Study AFT-MX-13b)

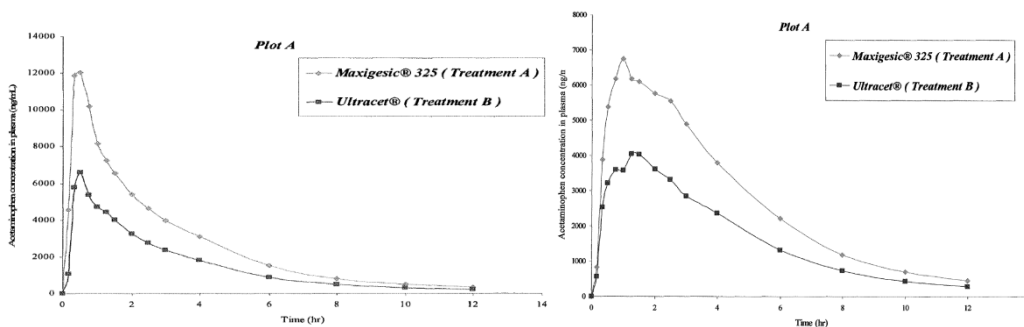
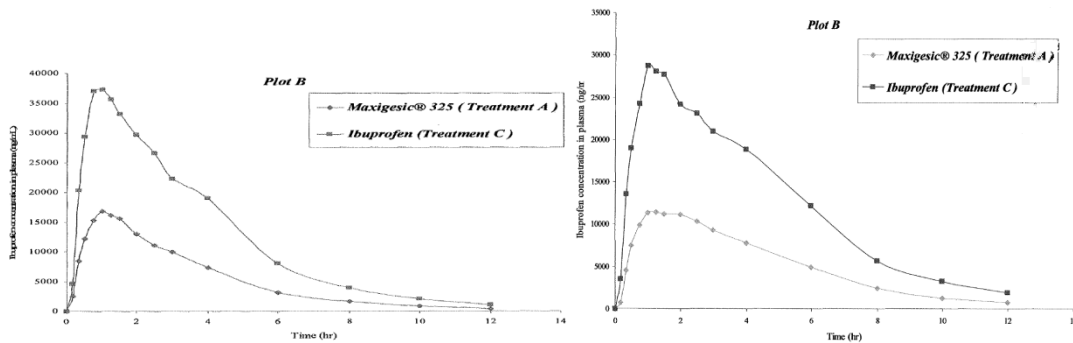


Figure 3 Mean Ibuprofen Plasma Concentration Versus Time for Treatment A (3 x FDC 325/97.5 tablets (total ibuprofen dose 292.5 mg)) and Treatment C (1 x Ibuprofen 800

mg tablet (total ibuprofen dose 800 mg)) under Fasting Condition (Left Panel) (Study AFT-MX-13a) and Fed Conditions (Right Panel) (Study AFT-MX-13b)



Descriptive statistics of PK parameters and BE analysis on dose normalized PK parameters are summarized in **Tables 1** and **2** in **Executive Summary**. Under fasting and fed conditions, 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) showed higher acetaminophen C_{max} and AUC values in comparison to 2 x Ultracet® tablets (650 mg dose of acetaminophen), and 1 x 800 mg ibuprofen tablet from Dr Reddys Laboratories (800 mg dose of ibuprofen) showed higher ibuprofen C_{max} and AUC values than 3 x FDC 325/97.5 tablets (292.5 mg dose of ibuprofen).

The dose normalized total exposures of acetaminophen (AUC_t/dose and AUC_{inf}/dose) for FDC 325/97.5 tablet and Ultracet® met the BE criteria under both fasting and fed conditions. The point estimates of the geometric mean ratios for acetaminophen AUC_t/dose and AUC_{inf}/dose were 115.58% and 114.57% under fasting condition and 109.31% and 108.99% under fed conditions, respectively. The corresponding 90% CIs were 111.68 – 119.62% and 110.74 – 118.54% under fasting condition and 107.12 – 111.55% and 106.89 – 111.13% under fed condition, respectively. All these 90% CIs fell within the 80 - 125% BE limit. Acetaminophen C_{max}/dose for FDC 325/97.5 tablet was 29% greater under fasting condition and met the BE criteria under fed condition.

The dose normalized total exposures of ibuprofen (AUC_t/dose and AUC_{inf}/dose) for FDC 325/97.5 tablet and the ibuprofen tablet from Dr Reddys Laboratories met the BE criteria under both fasting and fed conditions. The point estimates of the geometric mean ratios for ibuprofen AUC_t/dose and AUC_{inf}/dose were 115.05% and 115.03% under fasting condition and 114.20% and 113.33% under fed conditions, respectively. The corresponding 90% CIs were 110.73 – 119.47% and 110.81 – 119.41% under fasting condition and 110.44 – 118.09% and 109.68 – 117.09% under fed condition, respectively. All these 90% CIs fell within the 80 - 125% BE limit. Ibuprofen C_{max}/dose for FDC 325/97.5 tablet was 19% greater under fasting condition and met the BE criteria under fed condition.

Reviewer's Comment:

(1) The sponsor has submitted a Phase 3 pivotal study to demonstrate the safety and effectiveness of the FDC 325/97.5 tablet (AFT-MX-6), as well as three supportive studies (AFT-MX-1, AFT-MX-3 and AFT-MX-6E) with a higher dosage strength FDC 500/150 tablet. The sponsor stated that the safety and efficacy data for acetaminophen from Ultracet and Ibuprofen from Motrin to which the sponsor have PK bridging are intended to be supportive.

(2) Acetaminophen: Ultracet (acetaminophen 325 mg/tramadol HCl 37.5 mg) tablet (NDA 21-123) was selected as the list drug as it was the only prescription NDA Reference List Drug (RLD) product containing acetaminophen. The dose of acetaminophen from FDC 325/97.5 (3 tablets) used in the two PK bridging studies is higher than that in Ultracet tablets (2 tablets), being 975 mg vs. 650 mg, respectively. Additional Ultracet could not be given due to the dose-limiting side effects associated with the opioid component of this product. Three tablets of FDC 325/97.5 exhibited greater C_{max} and AUC values than 2 tablets of Ultracet under both fasting and fed condition. Because the acetaminophen from FDC 325/97.5 is being administered at less than the agency's maximum recommended daily dose for acetaminophen-containing products (4000 mg), this should not be a safety concern.

(3) Ibuprofen: Because the RLD Motrin (NDA 17-463) was discontinued (not for safety or efficacy reasons) and no longer available, the sponsor was advised that they could perform the PK bridging study with a generic ibuprofen product. Therefore, although the RLD is Motrin, the sponsor used the ibuprofen tablet from Dr Reddys Laboratories as the reference product in the PK bridging studies (AFT-MX-13a and AFT-MX-13b). Three tablets of FDC 325/97.5 exhibited less exposure than 1 tablet of ibuprofen tablet 800 mg under both fasting and fed conditions.

The oral bioavailability of ibuprofen from the proposed product FDC 325/97.5 tablet is similar to ibuprofen tablet from Dr Reddys Laboratories, based on dose-normalized values. BE was obtained for Dose-normalized AUC_t, AUC_{inf} and C_{max} in the fed state, and for AUC_t and AUC_{inf} under fasting conditions. There is a slightly (19%) higher dose-normalized fasting C_{max} for FDC 325/97.5 tablet. At the proposed dosing regimen, the daily dose of ibuprofen from FDC 325/97.5 (3 tablets Q6H) will provide ibuprofen dose of 1170 mg, which is 97.5% of the daily dose from approved dosing regimens of Motrin (e.g., 300 mg QID or 400 mg TID). The comparable systemic exposure to ibuprofen from proposed dosing regimen for FDC 325/97.5 and recommended doses of Motrin are expected considering the BE for dose-normalized ibuprofen AUC values. These data support the reliance of safety and efficacy findings from Motrin.

2. *What is the comparative bioavailability between 3 tablets of FDC 325/97.5 (total acetaminophen dose 975 mg and total ibuprofen dose 292.5 mg), and 2 tablets of FDC 500/150 (total acetaminophen dose 1000 mg and total ibuprofen dose 300 mg), 1 sachet (total acetaminophen dose 1000 mg and total ibuprofen dose 300 mg), and oral suspension (total acetaminophen dose 1000 mg and total ibuprofen dose 300 mg in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL])?*

FDC 325/97.5 Tablet vs FDC 500/150 Tablet: Acetaminophen AUC_t and AUC_{inf} from 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) and 2 x FDC 500/150 tablets (1000 mg dose of acetaminophen) met the BE criteria under both fasting and fed conditions. Acetaminophen C_{max} from 3 x FDC 325/97.5 tablets was 19% greater under fasting condition and met the BE criteria under fed condition. Ibuprofen C_{max}, AUC_t and AUC_{inf} from 3 x FDC 325/97.5 tablets (292.5 mg dose of ibuprofen) and 2 x FDC 500/150 tablets (300 mg dose of ibuprofen) met the BE criteria under both fasting and fed conditions.

Oral Suspension and Sachet vs FDC 325/97.5 Tablet: Acetaminophen and ibuprofen AUC_t and AUC_{inf} met BE criteria from Oral Suspension (1000 mg acetaminophen and 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]) and Sachet (1000 mg acetaminophen and 300 mg ibuprofen) versus that from 3 x FDC

325/97.5 tablets (975 mg dose of acetaminophen) under both fasting and fed conditions. Acetaminophen and ibuprofen C_{max} for oral suspension met BE criteria in comparison to FDC 325/97.5 tablet under fasting condition and was slightly lower (17% lower acetaminophen C_{max} and 15% lower ibuprofen C_{max}) under fed condition. Sachet exhibited 12% greater acetaminophen C_{max} and 34% greater ibuprofen C_{max} under fasting condition, but 26% lower acetaminophen and ibuprofen C_{max} under fed condition.

The comparative bioavailability of 3 x FDC 325/97.5 tablets (total dose of 975 mg acetaminophen and 292.5 mg ibuprofen), and 2 x FDC 500/150 tablets (total dose of 1000 mg acetaminophen and 300 mg ibuprofen), 1 sachet (1000 mg acetaminophen and 300 mg ibuprofen), and oral suspension (1000 mg acetaminophen and 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]) were determined in Studies AFT-MX-14a and AFT-MX-14b. Both studies were single dose, randomized, open-label, 4-way crossover study in healthy volunteers. AFT-MX-14a was conducted under fasting condition and AFT-MX-14b was conducted under fed condition. The following treatments were administered during the studies:

- **Treatment A:** Oral Suspension (total dose acetaminophen 1000 mg + ibuprofen 300 mg in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL])
- **Treatment B:** Sachet (1000 mg acetaminophen + 300 mg ibuprofen)
- **Treatment C:** 2 x FDC 500/150 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen)
- **Treatment D:** 3 x FDC 325/97.5 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen)

Treatment periods were separated by a 3-day washout period. Blood samples for pharmacokinetic determination were collected from each subject at pre-dose, and at 5, 15, 30, 45 min and at 1, 1.25, 1.5, 2, 3, 6, 8, 10, and 12-hour post dose. The mean acetaminophen plasma concentration-time profiles are shown in **Figure 6**. Ibuprofen plasma concentration-time profiles are presented in **Figure 7**.

Figure 6 Mean **Acetaminophen** Plasma Concentration Versus Time for Treatments A (Oral Suspension (total dose acetaminophen 1000 mg + ibuprofen 300 mg in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL])), B (Sachet (1000 mg acetaminophen + 300 mg ibuprofen)), C (2 x FDC 500/150 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen)), and D (3 x FDC 325/97.5 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen) under Fasting Condition (Left Panel) (Study AFT-MX-14a) and Fed Condition (Right Panel) (Study AFT-MX-14b)

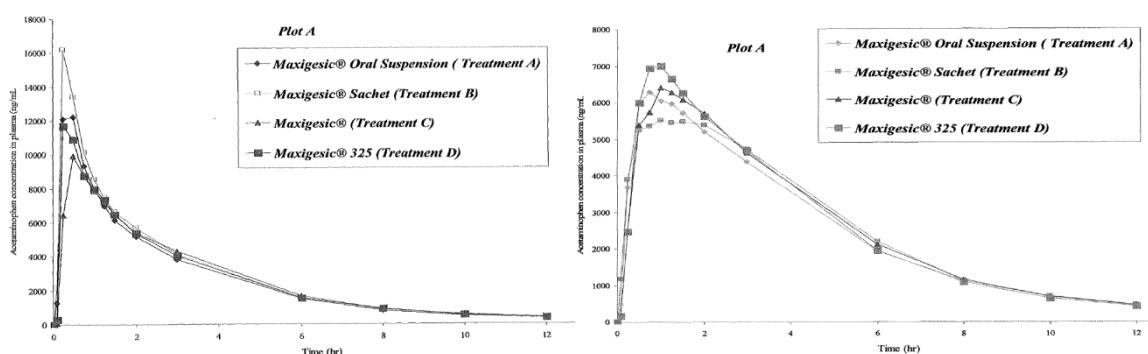
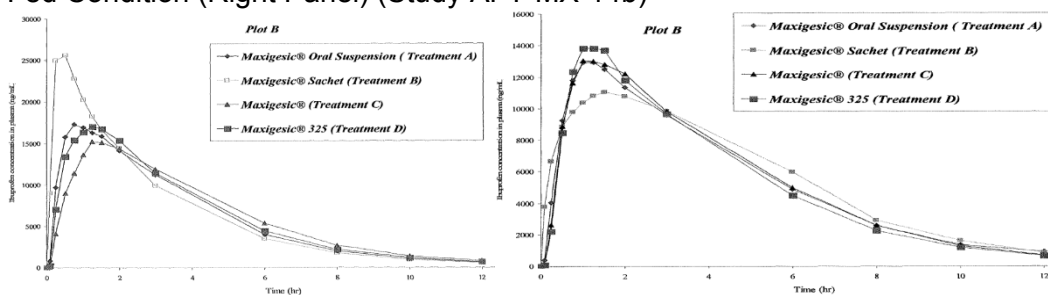


Figure 7 Mean **Ibuprofen** Plasma Concentration Versus Time for Treatments A (Oral Suspension (total dose acetaminophen 1000 mg + ibuprofen 300 mg in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL])), B (Sachet (1000 mg acetaminophen + 300 mg ibuprofen)), C (2 x FDC 500/150 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen)), and D (3 x FDC 325/97.5 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen) under Fasting Condition (Left Panel) (Study AFT-MX-14a) and Fed Condition (Right Panel) (Study AFT-MX-14b)



Tables 3 and 4 in Executive Summary summarized BE analysis on acetaminophen and ibuprofen PK for the comparison of FDC 325/97.5 tablets and FDC 500/150 tablets under fasting and fed conditions. The total exposures of acetaminophen AUCt and AUCinf from 3 x FDC 325/97.5 tablets and 2 x FDC 500/150 tablets met the BE criteria under both fasting and fed conditions. The point estimate of the geometric mean ratio (3 x FDC 325/97.5 tablets vs 2 x FDC 500/150 tablets) for acetaminophen AUCt and AUCinf were 102.49% and 102.92% under fasting condition and 100.33% and 99.77% under fed conditions, respectively. The corresponding 90% CIs were 99.35 – 105.73% and 99.74 – 106.21% under fasting condition and 97.04 – 103.74% and 96.63 – 103.02% under fed condition, respectively. All these 90% CIs fell within the 80 - 125% BE limit. Acetaminophen Cmax for 3 x FDC 325/97.5 tablets was 19% greater under fasting condition and met the BE criteria under fed condition.

Ibuprofen Cmax, AUCt and AUCinf for 3 x FDC 325/97.5 tablets and 2 x FDC 500/150 tablets met the BE criteria under both fasting and fed conditions. The point estimate of the geometric mean ratio (3 x FDC 325/97.5 tablets vs 2 x FDC 500/150 tablets) for ibuprofen Cmax, AUCt and AUCinf were 107.49%, 99.43%, and 98.99% under fasting condition and 101.415, 97.12% and 97.17% under fed conditions, respectively. The corresponding 90% CIs were 96.69 – 119.49%, 94.48 – 104.64%, and 94.35 – 103.85% under fasting condition and 90.45 – 113.69%, 94.36 – 99.97% and 94.31 – 100.12% under fed condition, respectively. All these 90% CIs fell within the 80 - 125% BE limit.

Tables 12 and 13 below summarized BE analysis on acetaminophen and ibuprofen PK for the comparison of oral suspension and FDC 325/97.5 tablet under fasting and fed conditions. Acetaminophen and ibuprofen AUCt and AUCinf met BE criteria from Oral Suspension (1000 mg acetaminophen and 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]) versus that from 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) under both fasting and fed conditions. Acetaminophen and ibuprofen Cmax for oral suspension are similar to FDC 325/97.5 tablet under fasting condition and slightly lower (17% lower acetaminophen Cmax and 15% lower ibuprofen Cmax) under fed condition.

Table 12 BE Analysis on **Acetaminophen** PK Parameters for Oral Suspension (total dose acetaminophen 1000 mg + ibuprofen 300 mg in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]) (Treatment A) and 3 x FDC 325/97.5 Tablets (Treatment D) under Fasting Condition (top panel) (AFT-MX-14a) and Fed Condition (bottom panel) (AFT-MX-14b)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	96.79	83.21	112.57	32.69
$AUC_{0 \rightarrow t}$	98.46	95.44	101.58	6.74
$AUC_{0 \rightarrow \infty}$	97.53	94.51	100.64	6.80

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	83.24	71.05	97.52	35.59
$AUC_{0 \rightarrow t}$	97.01	93.83	100.30	7.50
$AUC_{0 \rightarrow \infty}$	97.82	94.74	101.01	7.20

Source: Study AFT-MX-14a: Table 8; Study AFT-MX-14b: Table 8

Table 13 BE Analysis on **Ibuprofen** PK Parameters for Oral Suspension (total dose acetaminophen 1000 mg + ibuprofen 300 mg in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]) (Treatment A) and 3 x FDC 325/97.5 Tablets (Treatment D) under Fasting Condition (top panel) (AFT-MX-14a) and Fed Condition (bottom panel) (AFT-MX-14b)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	94.15	84.69	104.67	22.91
$AUC_{0 \rightarrow t}$	98.38	93.49	103.53	11.05
$AUC_{0 \rightarrow \infty}$	98.31	93.71	103.14	10.38

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	85.34	76.12	95.67	25.70
$AUC_{0 \rightarrow t}$	102.36	99.45	105.35	6.48
$AUC_{0 \rightarrow \infty}$	103.40	100.36	106.54	6.72

Source: Study AFT-MX-14a: Table 17; Study AFT-MX-14b: Table 17

Tables 14 and 15 below summarized BE analysis on acetaminophen and ibuprofen PK for Sachet (1000 mg acetaminophen + 300 mg ibuprofen) and 3 x FDC 325/97.5 tablets under fasting and fed conditions. Acetaminophen and ibuprofen AUC_t and AUC_{inf} met BE criteria from Sachet (1000 mg acetaminophen and 300 mg ibuprofen) versus that from 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) under both fasting and fed conditions. Sachet exhibited 12% greater acetaminophen C_{max} and 34% greater ibuprofen C_{max} under fasting condition, but 26% lower acetaminophen and ibuprofen C_{max} under fed condition.

Table 14 BE analysis on **Acetaminophen** PK Parameters for Sachet (1000 mg acetaminophen + 300 mg ibuprofen) (Treatment B) and 3 x FDC 325/97.5 Tablets (Treatment D) under Fasting Condition (top panel) (AFT-MX-14a) and Fed Condition (bottom panel) (AFT-MX-14b)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	112.47	96.70	130.82	32.69
$AUC_{0 \rightarrow t}$	107.71	104.41	111.12	6.74
$AUC_{0 \rightarrow \infty}$	106.53	103.23	109.93	6.80

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	74.53	63.61	87.32	35.59
$AUC_{0 \rightarrow t}$	99.47	96.21	102.85	7.50
$AUC_{0 \rightarrow \infty}$	100.08	96.93	103.33	7.20

Source: Study AFT-MX-14a: Table 9; Study AFT-MX-14b: Table 9

Table 15 BE Analysis on **Ibuprofen** PK Parameters for Sachet (1000 mg acetaminophen + 300 mg ibuprofen) (Treatment B) and 3 x FDC 325/97.5 Tablets (Treatment D) under Fasting Condition (top panel) (AFT-MX-14a) and Fed Condition (bottom panel) (AFT-MX-14b)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	134.05	120.58	149.02	22.91
$AUC_{0 \rightarrow t}$	105.03	99.80	110.53	11.05
$AUC_{0 \rightarrow \infty}$	104.28	99.40	109.40	10.38

Pharmacokinetic Parameter	90% Confidence intervals of parametric means			
	Point estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
C_{max}	74.27	66.25	83.26	25.70
$AUC_{0 \rightarrow t}$	106.71	103.68	109.83	6.48
$AUC_{0 \rightarrow \infty}$	107.67	104.50	110.94	6.72

Source: Study AFT-MX-14a: Table 18; Study AFT-MX-14b: Table 18

Reviewer's comment:

(1) When taken at full daily doses, the cumulative consumption of acetaminophen and ibuprofen from FDC 325/97.5 tablet is 3900 mg and 1170 mg, respectively. These acetaminophen and ibuprofen doses are 97.5% of those from FDC 500/150 tablet (4000 mg acetaminophen + 1200 mg ibuprofen).

(2) PK results showed that acetaminophen AUC_t and AUC_{inf} from 3 x FDC 325/97.5 tablets (975 mg dose of acetaminophen) and 2 x FDC 500/150 tablets (1000 mg dose of acetaminophen) met the BE criteria under both fasting and fed conditions. Acetaminophen C_{max} from 3 x FDC 325/97.5 tablets was 19% greater under fasting condition and met the BE criteria under fed condition. Ibuprofen C_{max}, AUC_t and AUC_{inf} from 3 x FDC 325/97.5 tablets (292.5 mg dose of ibuprofen) and 2 x FDC 500/150 tablets (300 mg dose of ibuprofen) met the BE criteria under both fasting and fed conditions.

(3) Similarity in acetaminophen and ibuprofen exposures between the FDC 325/97.5 tablet and FDC 500/150 tablet under fasting and fed conditions provided reasonable justification for the use of FDC 500/150 tablet data as supportive information for FDC 325/97.5 tablet.

3. What is the food effect on FDC 325/97.5 tablet?

High-fat meal had no effect on acetaminophen AUCs or ibuprofen C_{max} and AUCs except an approximately 30% decrease in acetaminophen C_{max}. Median T_{max} values for both acetaminophen and ibuprofen were slightly prolonged under fed conditions; 0.5 h (0.25, 3.00) fasting and 1.0 h (0.50, 3.00) fed for acetaminophen and 1.00 h (0.50, 12.00) fasting and 1.25 h (0.50, 3.00) fed for ibuprofen.

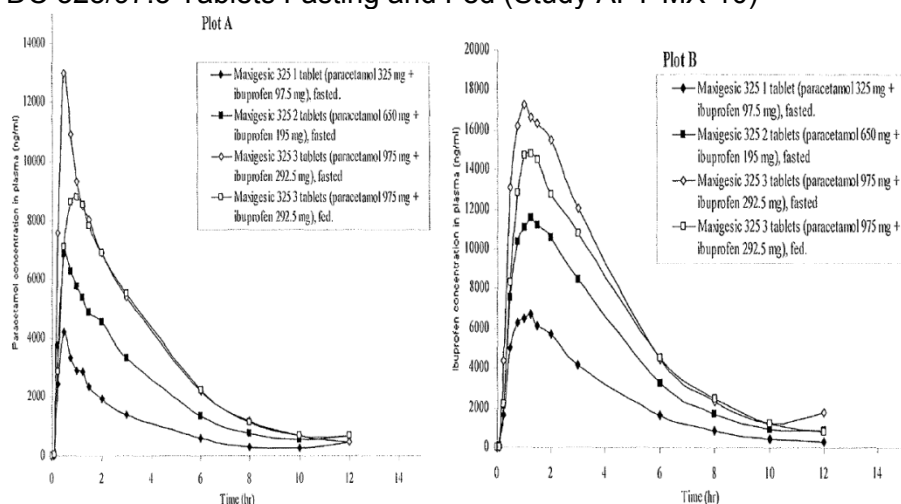
Study AFT-MX-10 was a single dose, randomized, open-label, 4-way crossover study evaluating the pharmacokinetic of different doses of FDC 325/97.5 tablet when taken as 1 tablet under fasting, as 2 tablets under fasting, and as 3 tablets under fasting and fed condition in healthy volunteers.

- **Treatment A:** 1 x FDC 325/97.5 tablet, fasted
- **Treatment B:** 2 x FDC 325/97.5 tablets, fasted
- **Treatment C:** 3 x FDC 325/97.5 tablets, fasted
- **Treatment D:** 3 x FDC 325/97.5 tablets, fed

Treatment periods were separated by a 7-day washout period. Blood samples for pharmacokinetic determination were collected from each subject at pre-dose, and at 5, 15, 30, 45 min and at 1, 1.25, 1.5, 2, 3, 6, 8, 10, and 12-hour post dose.

The mean acetaminophen (Plot A) and ibuprofen (Plot B) plasma concentration-time profiles are shown in **Figure 8**.

Figure 8 Mean Acetaminophen (Plot A) and Ibuprofen (Plot B) Plasma Concentration Versus Time for 1 x FDC 325/97.5 Tablet Fasting, 2 x FDC 325/97.5 Tablets Fasting, and 3 x FDC 325/97.5 Tablets Fasting and Fed (Study AFT-MX-10)



Descriptive statistics of PK parameters and BE analysis are summarized in **Table 5** in **Executive Summary**. High-fat meal had no effect on acetaminophen AUCs or ibuprofen Cmax and AUCs except an approximately 30% decrease in acetaminophen Cmax. Median Tmax values for both acetaminophen and ibuprofen were slightly prolonged under fed conditions; 0.5 h (0.25, 3.00) fasting and 1.0 h (0.50, 3.00) fed for acetaminophen and 1.00 h (0.50, 12.00) fasting and 1.25 h (0.50, 3.00) fed for ibuprofen.

4. Do acetaminophen and ibuprofen PKs increased dose proportionally with 1, 2, and 3 tablets of FDC 325/97.5?

Following a single dose administration of 1, 2, and 3 tablets of FDC 325/97.5 to healthy volunteers under fasting condition, acetaminophen and ibuprofen AUC values were dose proportional based on the analysis on log transformed AUC values using a power model.

In the previously described food effect Study AFT-MX-10, acetaminophen and ibuprofen PK following the administration of 1, 2, and 3 tablets of FDC 325/97.5 under fasting condition were determined (**Table 20**).

Table 20 Pharmacokinetics Parameters of Acetaminophen and Ibuprofen for 1 x FDC 325/97.5 Tablet (Treatment A), 2 x FDC 325/97.5 Tablets (Treatment B), and 3 x FDC 325/97.5 Tablets (Treatment C) under Fasting Condition (Study AFT-MX-10)

	PK parameter	1 x FDC 325/97.5 (Treatment A) (N = 27)	2 x FDC 325/97.5 (Treatment B) (N = 27)	3 x FDC 325/97.5 (Treatment C) (N = 27)
Acetaminophen	Cmax (ng/mL)	5417 (2211)	8757 (2501)	16548 (6746)
	Tmax (h)**	0.50 (0.25, 12)	0.75 (0.25, 12)	0.50 (0.25, 3.00)
	AUCt (ng.h/mL)	12060 (3980)	25295(7596)	40535 (12341)
	AUCinf (ng.h/mL)	12551 (3967)*	26503 (8136)	42655 (13218)*
	T1/2 (h)	3.77 (0.90)*	3.42 (0.96)	3.28 (1.24)*
Ibuprofen	Cmax (ng/mL)	8549 (2152)	14922 (4219)	21055 (3704)
	Tmax (h)**	1.00 (0.50, 3)	1.25 (0.75, 3)	1.00 (0.5, 12)
	AUCt (ng.h/mL)	28397 (8765)	53811 (16231)	78495 (21710)
	AUCinf (ng.h/mL)	29503 (9594)	55687 (17952)*	79772 (23565)*
	T1/2 (h)	2.31 (0.43)	2.32 (0.70)*	2.16 (0.36)*

*N = 26; ** median (min, max)

Source: Study AFT-MX-10: Tables 7, 8, 9, 21, 22, and 23in section 14.0 TABLES, FIGURES AND GRAPHS REFERRED To BUT NOT INCLUDED IN THE TEXT

Dose proportionality was assessed by power model described by Gough et al 1995 and Smith et al., 2000. Results of power model analyses on log-transformed AUCt, AUCinf, and Cmax showed that the slopes (1.11 for acetaminophen AUCt and AUCinf, 0.93 for ibuprofen AUCt, 0.91 for ibuprofen AUCinf) fell within the range of 0.80 to 1.25 and the corresponding 90% CI were contained within the predefined acceptance range. Thus, the AUCs for both acetaminophen and ibuprofen were dose proportional over the range of 1 to 3 tablets of FDC 325/97.5. Acetaminophen and ibuprofen Cmax values were roughly proportional with the slope of 0.98 and 0.82, respectively.

Table 21 Summary of Dose Proportionality Analysis for Log-Transformed Acetaminophen AUCt, AUCinf, and Cmax for 1, 2 and 3 Tablets of FDC 325/97.5 Using Power Model

Dose range Drug	Parameter	Slope	SE	90% CI	Critical Range Decision
97.5-292.5 Ibuprofen	AUC _{last}	0.926	0.003	0.9201 0.9299	0.796886 1.203114
97.5-292.5 Ibuprofen	AUC _{inf}	0.907	0.008	0.876 0.974	0.796886 1.203114
97.5-292.5 Ibuprofen	C _{max}	0.819	0.012	0.794492 0.842708	0.796886 1.203114
325-975 Paracetamol	AUC _{last}	1.111	0.025	1.051 1.149	0.796886- 1.203114
325-975 Paracetamol	AUC _{inf}	1.110	0.025	1.061 1.159	0.796886- 1.203114
325-975 Paracetamol	C _{max}	0.982	0.23	0.5292 1.4308	0.796886- 1.203114

Power model by (1) Gough et al., Assessment of Dose Proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK Joint Working Party. Drug Information Journal, 1995;29:1039-48 and (2) Smith et al., Confidence Interval criteria for assessment of dose proportionality. Pharmaceutical Research 2000;17(10):1278-83.

5. Was the proposed final to-be-marketed formulation used in clinical studies?

All clinical studies involving FDC 325/97.5 were conducted using the same formulation as that proposed for commercialization. The only difference between clinical test product and product proposed for commercialization is that the former were plain tablets and not embossed. The review of similarity in dissolution between clinical product and commercial product is deferred to Biopharm team.

2.6 Analytical Section

1. Are the bioanalytical methods adequately validated for determining plasma concentrations of acetaminophen and ibuprofen?

Validated LC-MS/MS methods were used for the determination of acetaminophen and ibuprofen in human plasma samples in all PK studies. The accuracy and precision are summarized in **Table 22**.

Table 22 Summary of Accuracy and Precision Data for Determination of Plasma Concentrations of Acetaminophen and Ibuprofen

Study	Analyte	Calibration Range	QC	QC Precision (%CV)	QC % Accuracy
AFT-MX-10	Acetaminophen	50-20000 ng/mL	150, 2500, 10000, and 15000 ng/mL	3.05 – 9.21%	-1.33 – 9.54%
	Ibuprofen	50-35000 ng/mL	150, 1250, 12500, 17500, and 27000 ng/mL	4.76 – 11.29%	-3.96 – 2.38%
AFT-MX-11	Acetaminophen	50-20000 ng/mL	150, 2500, 10000, and 15000 ng/mL	5.50 – 10.01%	-1.75 – 4.02%
	Ibuprofen	50-35000 ng/mL	150, 1250, 12500, 17500, and 27000 ng/mL	3.65 – 7.83%	-9.05 – -2.58%
AFT-MX-13a	Acetaminophen	50-20000 ng/mL	150, 2500, 10000, and 15000 ng/mL	5.54 – 7.71%	-6.13 – 1.62%
	Ibuprofen	50-35000 ng/mL	150, 1250, 12500, 17500, and 27000 ng/mL	2.95 – 4.87%	-4.75 – 4.88%
AFT-MX-13b	Acetaminophen	50-20000 ng/mL	150, 2500, 10000, and 15000 ng/mL	4.53– 6.11%	0.20 – 7.16%
	Ibuprofen	50-35000 ng/mL	150, 1250, 12500, 17500, and 27000 ng/mL	3.32 – 6.78%	-1.53 – 1.27%
AFT-MX-14a	Acetaminophen	50-20000 ng/mL	150, 2500, 10000, and 15000 ng/mL	8.19 – 9.52%	-4.06 – 1.45%
	Ibuprofen	50-35000 ng/mL	150, 1250, 12500, 17500, and 27000 ng/mL	3.51 – 5.23%	-2.66% - 4.76%
AFT-MX-14b	Acetaminophen	50-20000 ng/mL	150, 2500, 10000, and 15000 ng/mL	5.08-5.64%	-1.13 – 8.63%
	Ibuprofen	50-35000 ng/mL	150, 1250, 12500, 17500, and 27000 ng/mL	3.66 – 6.95%	-4.36 – 3.52%

Note: The bioanalytical reports are in the following locations in the NDA:

Study AFT-MX-10: 5.3.1.1 Study Report, Appendix 16.1.8 (pages 925-2027)

Study AFT-MX-11: 5.3.1.1 Study Report, Appendix 16.1.8 (pages 839-1941)

Study AFT-MX-13a: 5.3.1.1 Study Report, Appendix 16.1.8 (pages 668-882)

Study AFT-MX-13b: 5.3.1.1 Study Report, Appendix 16.1.8 (pages 660-871)

Study AFT-MX-14a: 5.3.1.1 Study Report, Appendix 16.1.8 (pages 902-1110)

Study AFT-MX-14b: 5.3.1.1 Study Report, Appendix 16.1.8 (pages 941-2026)

3 Detailed Labeling Recommendations

This product will not be approved during this review cycle and there is no labeling recommendation at this time.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	209471		Brand Name	Combogesic
OCP Division (I, II, III, IV, V)	II		Generic Name	Acetaminophen 325 mg/ibuprofen 97.5 mg
Medical Division	DAAAP		Drug Class	NSAID
OCP Reviewer	Wei Qiu, Ph.D.		Indication(s)	Short term management of mild to moderate acute pain
OCP Team Leader	Yun Xu, Ph.D.		Dosage Form	Oral tablet
Date of Submission	Mar 1, 2017		Dosing Regimen	3 tablets Q6H as needed for pain relief, up to a maximum of 12 tablets per day
Estimated Due Date of OCP Review	Nov 13, 2017		Route of Administration	Oral
Medical Division Due Date	Nov 27, 2017		Sponsor	AFT Pharmaceuticals
PDUFA Due Date	Jan 1, 2018 (12/29/17)		Priority Classification	Standard
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		AFT-MX-10
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x	3		AFT-MX-9, AFT-MX-11 (FDC 500/150), and AFT-MX-8 (FDC 500/150)
In-vitro:	x	1		(b) (4) Human Enzyme Study
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				

Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	2		AFT-MX-13a and AFT-MX-13b
Bioequivalence studies -				
traditional design: single / multi dose:				
replicate design: single / multi dose:				
Food-drug interaction studies	x	(1)		AFT-MX-10
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Sponsor stated that the FDC 325/97.5 product used in all clinical studies have the same formulation as the proposed commercial product. The only difference is the clinical products were plain tablets and not embossed. Biopharm team will review the dissolution data for the clinical product and commercial product.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Sponsor submitted plasma concentration time dataset as well as pharmacokinetic parameter datasets in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Agency agreed with the sponsor's iPSP in the communication dated 2/6/2017. The sponsor requested deferral of all assessments of safety and effectiveness of Combogesic in the age-group 12-17 yrs and of Combogesic oral suspension (b) (4) 2 yrs and between the ages of 2 and 11 yrs.
16	Did the applicant submit all the pediatric			x	

	exclusivity data, as described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

This NDA submission is fillable from clinical pharmacology perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- (1) The comparative bioavailability studies AFT-MX-13a and AFT-MX-13b suggest that the oral bioavailability of acetaminophen and ibuprofen from the proposed product FDC 325/97.5 are similar to the listed drug products, Ultracet (NDA 21-123) and Ibuprofen tablet (ANDA 75,682), based on dose normalized AUC values. Therefore, FDC 325/97.5 at the proposed dosing regimen will result in higher acetaminophen exposure than the maximal labeled dose for Ultracet and lower ibuprofen exposure than the maximal labeled dose for Ibuprofen tablet. Provide your justification how you can rely on the safety and efficacy findings from the identified listed drug products, Ultracet and Ibuprofen tablet.
- (2) You proposed to use pharmacokinetic data obtained from FDC 500/150 as supportive information in the NDA for FDC 325/97.5. Provide the justification how you can use these data to support FDC 325/97.5.
- (3) Conduct dose proportionality analyses for 1, 2, and 3 tablets of FDC 325/97.5 in Study AFT-MX-10 using a power model or bioequivalence approach.

AFT Pharmaceuticals submitted a 505(b) (2) NDA Combogesic (acetaminophen 325 mg/ibuprofen 97.5 mg) tablet for the short term management of mild to moderate acute pain. Throughout the drug development process, FDC 325/97.5 has been used.

As a 505(b)(2) application, the sponsor plans to rely in part on the agency's finding of the safety and efficacy of Ultracet tablet (acetaminophen 325 mg/tramadol HCl 37.5 mg) (NDA 21-123) and Ibuprofen tablet (400, 600, and 800 mg) (ANDA 75,682).

The sponsor conducted an in vitro drug interaction study ((b) (4) human enzyme study) to evaluate the effects of fixed combination of acetaminophen and ibuprofen on CYP1A, 2C9, 2C19, 2D6, 2E1, and 3A.

The PK data supporting this NDA are generated from 4 PK studies using FDC 325/97.5 (AFT-MX-9 (pilot PK DDI study), AFT-MX-10 (dose proportionality and food effect), AFT-MX-13a (comparative bioavailability in comparison with Ultracet and Ibuprofen tablet under fasting condition), and AFT-MX-13b (comparative bioavailability in comparison with Ultracet and Ibuprofen tablet under fed condition)). The sponsor conducted a pivotal Phase 3 study AFT-MX-6 using FDC 325/97.5 product.

In addition, the sponsor provided studies with Maxigesic (acetaminophen 500 mg/ibuprofen 150 mg, also known as FDC 500/150) as supportive information (PopPK analyses on AFT-MX-1, AFT-MX-11 (DDI and food effect), AFT-MX-8 (NAPQI study – effect of ibuprofen on acetaminophen), DOS-MOD (modeling report of dose response), INT-SIM (interaction-simulation study), and 3 Phase 3 studies.

4.2 Individual Study Synopsis

4.2.1 Study AFT-MX-8 (NAPQI Study)

Name of Sponsor: AFT Pharmaceuticals Ltd.	Individual Study Table Referring to Part of the Dossier: Module: 5.3.1	(For National Authority Use only)
Name of Finished Product: Maxigesic® tablets.		
Name of Active Ingredient: Paracetamol 500 mg + ibuprofen 150 mg.		
Title of Study: Single-Centre, Single-Dose, Open-Label, Randomised, Cross-Over Study Of The Effect Of Ibuprofen On The Oxidative Metabolism Of Paracetamol When Administered As A Fixed Dose Combination (Maxigesic®) In Healthy Volunteers Under Fasting Conditions		
Study Director: N. Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, Chairman of International Pharmaceutical Research Center, Jordan. Principal Investigator: Abdullah Hiyari, M.D., M.R.C.P., International Pharmaceutical Research Center, Jordan.		
Study Centres: International Pharmaceutical Research Center, Jordan.		
Publication: Not yet submitted for publication		
Study Period (years): Date of first dose: 09 September 2012 Date of last follow-up: 17 September 2012	Phase of Development: Phase I	
Objectives: To identify the effect of ibuprofen on the oxidative metabolism of paracetamol when administered as a fixed dose combination in the ratio of Maxigesic® [paracetamol 500 mg + ibuprofen 150 mg].		
Methodology: A single dose, open label, randomised, cross-over design on 12 healthy volunteers under fasting conditions. Urine samples were collected pre-dose and over 0-1, 1-2, 2-4, 4-6, 6-8, 8-12 and 12-24 hours. Assays of paracetamol and its metabolites (glutathione-paracetamol, cysteine-paracetamol, mercapturate-paracetamol, glucuronide-paracetamol and sulfate-paracetamol) were carried out in the laboratories of the IPRC using a validated LC/MS/MS and HPLC chromatographic method developed specifically for the determination paracetamol and its metabolites in urine [see Appendix 16.1.8].		

Name of Sponsor: AFT Pharmaceuticals Ltd.	Individual Study Table Referring to Part of the Dossier Module: 5.3.1	(For National Authority Use only)
Name of Finished Product: Maxigesic® tablets.		
Name of Active Ingredient: Paracetamol 500 mg + ibuprofen 150 mg.		
Number of Participants: A total of 12 subjects were planned and enrolled. All 12 subjects completed both study periods. The data of twelve completing subjects were taken for the pharmacokinetic and statistical evaluations.		
Diagnosis and Main Criteria for Inclusion: Healthy volunteers with the age range between 18 and 50 years with the body mass index (BMI) between 18.5 and 30.0 kg/m ² , having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria		
Test Product(s), Dose and Mode of Administration: Paracetamol 500 mg + ibuprofen 150 mg tablets (Maxigesic® tablets) by oral route, two tablets as a single dose with 240 ml of water		
Duration of Treatment: Single dose in both periods, with a wash out period of 7 days from the completion of dosing in one period to the start of dosing in the next period.		
Reference Therapy, Dose and Mode of Administration: Paracetamol 500 mg (Panadol®), 2 tablets, administered orally with 240 ml of water		

Name of Sponsor: AFT Pharmaceuticals Ltd.	Individual Study Table Referring to Part of the Dossier Module: 5.3.1	(For National Authority Use only)
Name of Finished Product: Maxigesic® tablets.		
Name of Active Ingredient: Paracetamol 500mg + ibuprofen 150mg.		

Statistical Methods:
The total amount (X_{ut}) and maximum rate of excreted (R_{max}) paracetamol and its metabolites were calculated. Data was summarised using descriptive statistics, including means, medians, geometric means, standard deviations, inter-quartile ranges and ranges. The total amounts excreted (X_{ut}) and the maximum rate of excretion (R_{max}) was compared between treatments using ANOVA. The ANOVA included terms for subject, sequence, period and treatment. A two-tailed p-value <0.05 was taken to indicate statistical significance and 90% confidence intervals on the differences were calculated using the residual mean squares from the ANOVA models. The data was log-transformed prior to analyses, and confidence intervals back-transformed to represent the ratios of treatments.
Additionally, for each treatment the percentage contribution of paracetamol and its metabolites to the total amount excreted were calculated from the log-transformed data and are shown as back-transformed estimates with 95% confidence intervals.

Criteria Evaluation:
 X_{ut} and R_{max} were considered the *primary pharmacokinetic parameters*, while t_{max} and AURC were defined as *secondary pharmacokinetic parameters*. Pharmacokinetic parameters were calculated as follows using the Kinetica™ 2000 Computer Program:

X_u	The amount of drug excreted during each urine collection interval
X_{ut} :	The total amount of drug excreted in the urine over the entire period of sample collection
R_e :	Rate of drug excretion
R_{max} :	The maximum urinary excretion rate
t_{max} :	Time of maximum urinary excretion rate
AURC:	The accumulated area under the urinary excretion rate curve.

Safety Assessments Analysis:
Safety was evaluated during each study period, and for 7 days following the study drug administration. An acute safety evaluation was performed during each study period by recording spontaneously reported AEs and by clinical assessments.
Known NSAID adverse events (i.e. GI ulceration, indigestion/stomach pain, GI bleeding, bronchospasm, water retention, renal failure, skin reactions and thromboembolic events), and known paracetamol adverse effects (i.e. clinical evidence of hepatotoxicity) were compared between groups.
AEs were assessed up to 7 days after the last dose of the study medication by spontaneous reporting and at a final follow-up phone call.

SUMMARY – CONCLUSIONS

PRIMARY AND SECONDARY PHARMACOKINETICS:

The results of this study indicated that the amounts of total urinary excretion of paracetamol from the Maxigesic® formulation is comparable to that excreted from the Panadol® formulation when two tablets of each formulation were administered in the fasted state. This conclusion is based on the finding that the total amounts of paracetamol and paracetamol related metabolites eliminated in the urine (X_{ut}) were similar as reflected in a relative total amount of paracetamol (103.0%).

The study results also indicated that the relative amounts of paracetamol metabolites eliminated in urine were similar for the Maxigesic® and Panadol® formulations and these amounts were similar to results obtained in previous studies of paracetamol and metabolites appearing in the literature (Gelotte et al, 2007; Tanner et.al, 2010, Slattery et. al 1981, Prescott LF et.al, 1983).

Statistical comparison of both primary (X_{ut} , R_{max}) and secondary (T_{max} , AURC) pharmacokinetic parameters produced very similar estimates for the two study treatments, although the inter and intra-subject variability was large as is typical for excretion estimates and therefore precise estimates of equivalence were not produced.

The analyses indicate that there are no clinically relevant differences in the elimination and oxidative metabolism of paracetamol when administered in combination with ibuprofen doses in the amounts contained in Maxigesic®.

SAFETY RESULTS:

Clinical assessment for all subjects was carried out to evaluate their tolerability to the study's medications. No serious adverse events occurred during the study. Both study medications provided throughout the two study periods were safe and well tolerated.

CONCLUSION:

The maximum urinary excretion rate (R_{max}), the total amount of drug excreted in the urine over the entire period of sample collection (X_{ut}) and secondary (T_{max} , AURC) pharmacokinetic parameters of paracetamol and its related metabolites were comparable between the two study treatments. The amount of paracetamol undergoing oxidative metabolism was not significantly altered by the concomitant administration of ibuprofen (as a fixed combination in the amounts contained in Maxigesic®).

The total amount of paracetamol and its related metabolites (glutathione-paracetamol, cysteine-paracetamol, mercapturate-paracetamol, glucuronide-paracetamol and sulfate-paracetamol) excreted in urine over the entire period of sample collection showed a significant amount of inter and intra-patient variation. There were minor differences between the two study treatments but the differences were not considered to be clinically significant.

Date of the report: 28/03/13

4.2.2 Study AFT-MX-10 (Food Effect and Dose Proportionality)

2.0 STUDY SYNOPSIS

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART (S) 1. ETHICS 2. INTRODUCTION 3. INVESTIGATION
(Treatment A) Maxigesic 325, 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), fasted	
(Treatment B) Maxigesic 325, 2 tablets (paracetamol 650 mg + ibuprofen 195 mg), fasted	
(Treatment C) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fasted	
(Treatment D) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fed	
STUDY TITLE	Single Centre, Single-Dose, Open-Label, Randomized, Four-Way Cross-Over Study Evaluating The Pharmacokinetics Of Paracetamol Plus Ibuprofen (Maxigesic 325) In 28 Healthy Volunteers Under Fasting And Fed Conditions.
IPRC PROTOCOL CODE NO.	ACIB-T002
IPRC STUDY CODE	ACIB-AFT-T0713/926
INSTITUTIONAL REVIEW BOARD	Institutional Review Board of IPRC, Jordan.
INVESTIGATORS	Study Director: Naji Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, International Pharmaceutical Research Center, Jordan. Principal Investigator: Abdullah Hiyari, M.D., M.R.C.P., International Pharmaceutical Research Center, Jordan. Study Physician: Usama Harb, M.D., International Pharmaceutical Research Center, Jordan.
STUDY CENTRE	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan.
STUDY PERIODS	Screening: 04/12/2013 Dosing Period II: 23/12/2013 Enrolment: 15/12/2013 Dosing Period III: 30/12/2013 Dosing Period I: 16/12/2013 Dosing Period IV: 06/01/2014 First Sample Collected: 16/12/2013 Last sample Collected: 06/01/2014
PHASE OF DEVELOPMENT	Phase I – Pharmacokinetic Study

SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S) 3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
(Treatment A) Maxigesic 325, 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), fasted	
(Treatment B) Maxigesic 325, 2 tablets (paracetamol 650 mg + ibuprofen 195 mg), fasted	
(Treatment C) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fasted	
(Treatment D) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fed	
OBJECTIVES	Primary Objectives: - To evaluate the pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow \infty}$, T_{max} and $t_{1/2}$) of different doses of Maxigesic 325 when taken as 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), as 2 tablets (paracetamol 650 mg + ibuprofen 195 mg) and as 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg). - To describe the effect of food on the pharmacokinetic profile of Maxigesic 325 when taken as 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg). Secondary Objective: - To monitor the safety and tolerability of the different doses of Maxigesic 325 under fasting and fed conditions.
CLINICAL LABORATORY	IPRC clinical laboratory
ANALYTICAL SITE	(b) (4)
BIOANALYTICAL METHODOLOGY	LC/MS/MS Detector with LLOQ = 50.000 ng/ml for paracetamol and LC/MS/MS detector, with LLOQ= 50.000 ng/ml for ibuprofen.
STUDY SUBJECTS	The study protocol called for 28 healthy subjects, 28 subjects were dosed and 27 subjects completed the crossover.
DEMOGRAPHIC DATA (N=28)	Gender: Males Age: 29 ± 6.81 year Height: 175 ± 7.18 cm Weight: 79 ± 11.00 Kg BMI: 25.6 ± 3.04 Kg/m ²
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male subjects with the age range between 18 and 40 years, with the body mass index (BMI) between 18.5 and 30.0 kg/m ² , having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria.

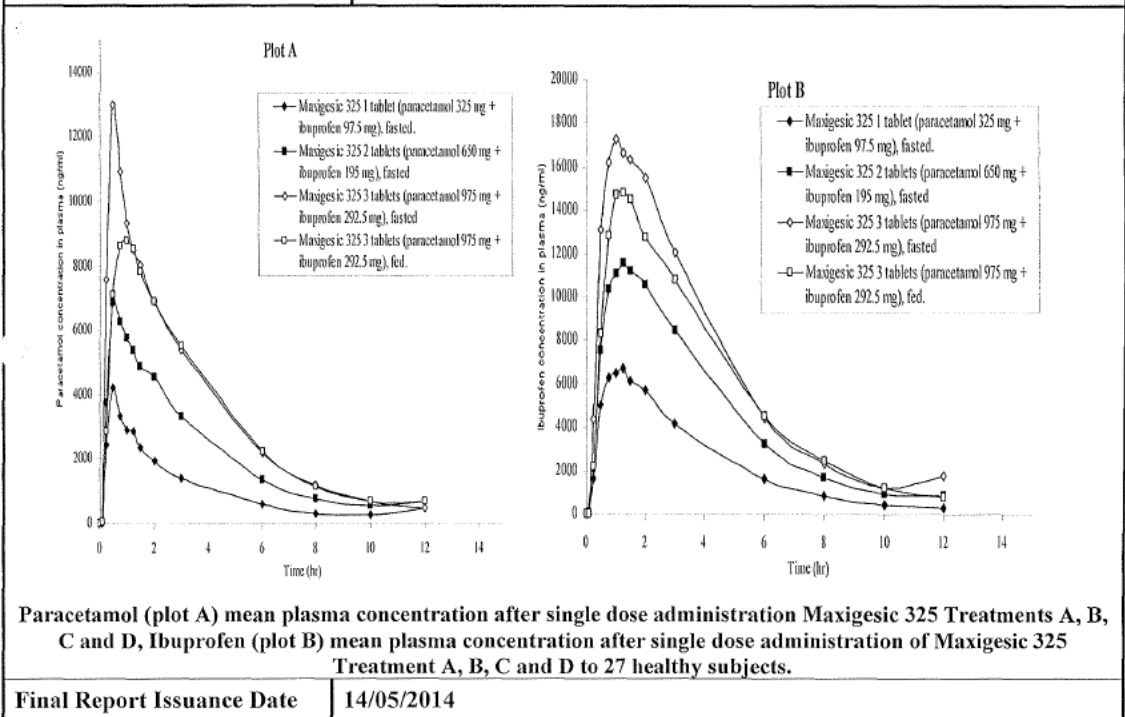
SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S)
(Treatment A) Maxigesic 325, 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), fasted	
(Treatment B) Maxigesic 325, 2 tablets (paracetamol 650 mg + ibuprofen 195 mg), fasted	
(Treatment C) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fasted	
(Treatment D) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fed	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
DOSAGE REGIMEN	(Treatment A): Single-Dose, Maxigesic 325, 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), fasted. Batch No. BAD1201B, Expiry Date: 01/15. (Treatment B): Single-Dose, Maxigesic 325, 2 tablets (paracetamol 650 mg + ibuprofen 195 mg), fasted. Batch No. BAD1201B, Expiry Date: 01/15. (Treatment C): Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fasted. Batch No. BAD1201B, Expiry Date: 01/15. (Treatment D): Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fed. Batch No. BAD1201B, Expiry Date: 01/15.
ADMISSION AND CONFINEMENT	Subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, and confined until 12-hour sample was collected. Subjects that were allocated to treatments A, B or C were required to fast overnight (for at least 10 hours) and for four hours after dosing. Subjects that were allocated to receive treatment D were fasting for at least 10 hours overnight. Thirty minutes before administration of the study drug the subjects received a standardised breakfast and no additional food was allowed for at least 4 hours post dosing
DRUG ADMINISTRATION	Each subject received an oral dose of the assigned treatment, according to a randomization scheme, administered with 240 ml water.
WASHOUT PERIOD	Seven-days between each two consecutive study drug administration.
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory tests, ECG, physical examination and vital signs.
BLOOD SAMPLING SCHEDULE	Fourteen blood samples were drawn at 0.00 (one pre-dose sample), 5, 15, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 3.00, 6.00, 8.00, 10.00 and 12.00 hours (post-dose) in each period. The total volume of blood draws did not exceed 403.5 ml.

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S)
(Treatment A) Maxigesic 325, 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), fasted	5. RESULTS AND BIOEQUIVALENCE EVALUATION
(Treatment B) Maxigesic 325, 2 tablets (paracetamol 650 mg + ibuprofen 195 mg), fasted	
(Treatment C) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fasted	
(Treatment D) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fed	
BLOOD SAMPLES HANDLING	
CLINICAL SAMPLES STORAGE	The blood samples for Paracetamol and Ibuprofen were collected in lithium heparinized tubes, centrifuged and the resulting plasma samples were immediately stored.
SAFETY AND TOLERABILITY	Plasma samples were stored under a nominal temperature of -70°C until analyzed.
PHARMACOKINETIC PARAMETERS	All treatments were safe and well tolerated.
STATISTICAL METHODS	C_{max} , $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, t_{max} and $t_{1/2}$
BIOAVAILABILITY OF THE FED VS. FAST PK PARAMETERS	ANOVA using 5% significance level for logarithmically transformed (with the 90% confidence intervals) C_{max} , $AUC_{0 \rightarrow t}$, and $AUC_{0 \rightarrow \infty}$. ANOVA using 5% significance level for no logarithmically transformed (with the 90% confidence intervals) $t_{1/2}$. t_{max} was compared using Wilcoxon signed-rank tests.
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Dose proportionality for C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ parameters, for both paracetamol and ibuprofen. For dose proportionality to be shown P-values should be < 0.05. Confidence intervals of logarithmically transformed Treatment D/Treatment C ratios within 80-125% for C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$.
	Confidence Intervals for $t_{1/2}$ of Paracetamol for the un-transformed Treatments A, B and C Ratios of: $t_{1/2}$ (C and A) (101.53-128.63) % $t_{1/2}$ (C and B) (90.75-117.85) % $t_{1/2}$ (B and A) (97.34-123.33) % Confidence Intervals for Paracetamol for the log-transformed (Treatment D) / (Treatment C) Ratios of: C_{max} 72.78 (63.00-84.08) % $AUC_{0 \rightarrow t}$ 93.83 (89.54-98.31) % $AUC_{0 \rightarrow \infty}$ 93.84 (90.61-97.18) %

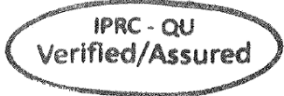
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Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S)
(Treatment A) Maxigesic 325, 1 tablet (paracetamol 325 mg + ibuprofen 97.5 mg), fasted	
(Treatment B) Maxigesic 325, 2 tablets (paracetamol 650 mg + ibuprofen 195 mg), fasted	
(Treatment C) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fasted	
(Treatment D) Maxigesic 325, 3 tablets (paracetamol 975 mg + ibuprofen 292.5 mg), fed	
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	5. RESULTS AND BIOEQUIVALENCE EVALUATION Confidence Intervals for $t_{1/2}$ of Ibuprofen for the un-transformed Treatments A, B and C Ratios of: $t_{1/2}$ (C and A) (98.81-115.68) % $t_{1/2}$ (C and B) (99.07-115.94) % $t_{1/2}$ (B and A) (91.91-107.60) % Confidence Intervals for Ibuprofen for the log-transformed (Treatment D) / (Treatment C) Ratios of: C_{max} 88.87 (81.17-97.29) % $AUC_{0 \rightarrow t}$ 88.01 (84.24-91.93) % $AUC_{0 \rightarrow \infty}$ 89.88 (86.12-93.79) %
CONCLUSIONS	Dose proportionality was determined for C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ parameters, for both paracetamol and ibuprofen. For paracetamol, it was found that the P-value of $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ was < 0.05 while for C_{max} the P-value was not < 0.05 with a high linearity as the regression values for all three parameters was more than 0.98. For ibuprofen, it was found that the P-value of C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ was < 0.05 with a high linearity as the line regression values for all three parameters were more than 0.98 The above suggest the dose proportionality for both paracetamol and ibuprofen.

CONCLUSIONS	Also the difference between fasting and fed means of Treatment C and Treatment D indicates the presence of food effect on the bioavailability of paracetamol since the 90% Confidence Intervals for paracetamol transformed ratios (Test/Reference) were not within the accepted limits of 80.00 % - 125.00 % for C_{max} but within the accepted limits of 80.00 % - 125.00 % for $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ and the absence of food effect on the bioavailability of ibuprofen since the 90% Confidence Intervals for ibuprofen transformed ratios (Test/Reference) were within the accepted limits of 80.00 % - 125.00 % for C_{max}, $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$. Food had an effect on the extent of absorption for both paracetamol $AUC_{0 \rightarrow \infty} = 40158.5$ ng.h/ml (fed) vs.42655.0 ng.h/ml (fast) and ibuprofen $AUC_{0 \rightarrow \infty} = 71509.7$ ng.h/ml (fed) vs.79771.8 ng.h/ml. The rate of absorption was significantly prolonged for paracetamol ($t_{max} = 1.14 \pm 0.68$ hours [fed] vs. 0.68 ± 0.58 hours [fast]) but not for ibuprofen. Peak plasma concentrations were significantly decreased for paracetamol ($C_{max} = 11723.549$ ng/ml (fed) vs. 16548.360 ng/ml (fast) as well as for ibuprofen, but not significantly ($C_{max} = 19082.730$ ng/ml (fed) vs. 21055.07 ng/ml (fast)).
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4.2.3 Study AFT-MX-11 (DDI)

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART (S) 1. ETHICS 2. INTRODUCTION 3. INVESTIGATION 
(Treatment A) 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted	
(Treatment B) 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted	
(Treatment C) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted	
(Treatment D) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed	
STUDY TITLE	Single Centre, Single-Dose, Open-Label, Randomized, Four-Way Cross-Over Study Evaluating The Pharmacokinetics Of Maxigesic® (Paracetamol 500 mg + Ibuprofen 150 mg) In 28 Healthy Volunteers Under Fasting And Fed Conditions.
IPRC PROTOCOL CODE NO.	ACIB-T003
IPRC STUDY CODE	ACIB-AFT-T1213/972
INSTITUTIONAL REVIEW BOARD	Institutional Review Board of IPRC, Jordan.
INVESTIGATORS	Study Director: Naji Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, International Pharmaceutical Research Center, Jordan. Principal Investigator: Abdullah Hiyari, M.D., M.R.C.P., International Pharmaceutical Research Center, Jordan. Study Physician: Usama Harb, M.D., International Pharmaceutical Research Center, Jordan.
STUDY CENTRE	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan.
STUDY PERIODS	Screening: 25/01/2014 Enrolment: 01/02/2014 Dosing Period I: 02/02/2014 First Sample Collected: 02/02/2014 Dosing Period II: 09/02/2014 Dosing Period III: 16/02/2014 Dosing Period IV: 23/02/2014 Last sample Collected: 23/02/2014

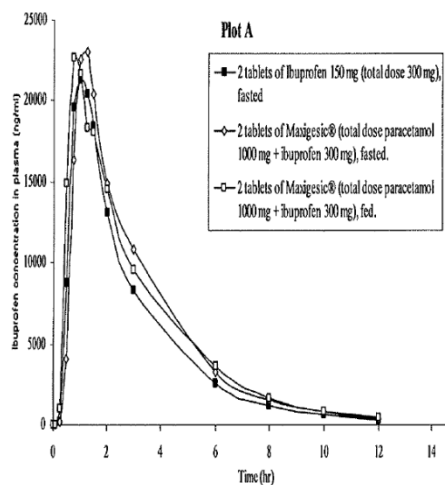
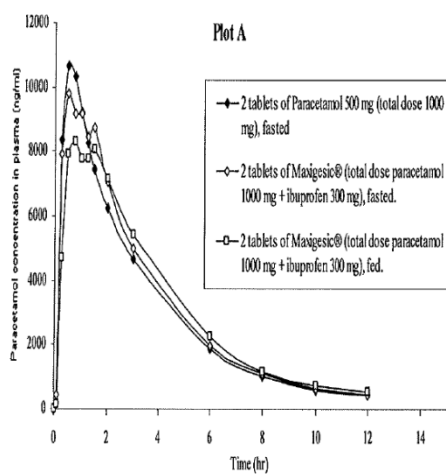
SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S) 3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS IPRC - QU Verified/Assured
(Treatment A) 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted	
(Treatment B) 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted	
(Treatment C) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted	
(Treatment D) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed	
PHASE OF DEVELOPMENT	Phase I – Bioavailability Study.
OBJECTIVES	Primary Objectives: - To evaluate the pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow \infty}$, $AUC_{0 \rightarrow t}$, T_{max} and $t_{1/2}$) of 1000 mg paracetamol and 300 mg ibuprofen, when taken alone, or when taken in combination as 2 tablets of Maxigesic®, under fasting conditions - To describe the effect of food on the pharmacokinetic profile of Maxigesic® when taken as 2 tablets (total dose paracetamol 1000 mg + ibuprofen 300 mg). Secondary Objective: To monitor the safety and tolerability of Maxigesic® under fasting and fed conditions.
CLINICAL LABORATORY	IPRC clinical laboratory.
ANALYTICAL SITE	(b) (4)
BIOANALYTICAL METHODOLOGY	LC/MS/MS Detector with LLOQ = 50.000 ng/ml for paracetamol and HPLC/UV detector, with LLOQ= 50.000 ng/ml for ibuprofen.
STUDY SUBJECTS	The study protocol called for 28 healthy subjects, 28 subjects were dosed and 26 subjects completed the crossover.
DEMOGRAPHIC DATA (N=28)	Gender: Males Age: 28 ± 6.51 year Height: 172 ± 6.79 cm Weight: 76 ± 8.18 Kg BMI: 25.5 ± 3.07 Kg/m ²

SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S)
(Treatment A) 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted	
(Treatment B) 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted	
(Treatment C) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted	
(Treatment D) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	
DOSEAGE REGIMEN	Healthy male subjects with the age range between 18 and 40 years with the body mass index (BMI) between 18.5 and 30.0 kg/m², having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria. (Treatment A): Single-Dose, 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted. Batch No. MGPGE 1001, Expiry Date: 05/14. (Treatment B): Single-Dose, 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted. Lot No. MGIGE 1001, Expiry Date: 05/14. (Treatment C): Single-Dose, 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted. Batch No. MWGE2003, Expiry Date: 07/15. (Treatment D): Single-Dose, 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed. Batch No. MWGE 2003, Expiry Date: 07/15.
ADMISSION AND CONFINEMENT	Subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, and confined until 12-hour sample was collected. Subjects allocated to treatment D (fed condition) received thirty minutes prior to the study drug administration a standardised breakfast and no additional food was allowed for at least 4 hours post-dosing.
DRUG ADMINISTRATION	Each subject received an oral dose of the assigned treatment, according to a randomization scheme, administered with 240 ml water.

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Paracetamol and Ibuprofen	TABLE REFERENCE PART(S)
(Treatment A) 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted	5. RESULTS AND PK/BIOEQUIVALENCE EVALUATION
(Treatment B) 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted	
(Treatment C) 2 tablets of Maxigesic [®] (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted	
(Treatment D) 2 tablets of Maxigesic [®] (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed	
WASHOUT PERIOD	Seven-days between each two consecutive study drug administration.
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory tests, ECG, physical examination and vital signs.
BLOOD SAMPLING SCHEDULE	Fourteen blood samples were drawn at 0.00 (one pre-dose sample), 5, 15, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 3.00, 6.00, 8.00, 10.00 and 12.00 hours (post-dose) in each period. The total volume of blood draws did not exceed 403.5 ml.
BLOOD SAMPLES HANDLING	The blood samples for Paracetamol and Ibuprofen were collected in lithium heparinized tubes, centrifuged and the resulting plasma samples were immediately stored.
CLINICAL SAMPLES STORAGE	Plasma samples were stored under a nominal temperature of -70°C until analyzed.
SAFETY AND TOLERABILITY	All treatments were safe and well tolerated.
PHARMACOKINETIC PARAMETERS	C_{max} , $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, t_{max} and $t_{1/2}$
STATISTICAL METHODS	ANOVA using 5% significance level for logarithmically transformed (with the 90% confidence intervals) C_{max} , $AUC_{0 \rightarrow t}$, and $AUC_{0 \rightarrow \infty}$. ANOVA using 5% significance level for no logarithmically transformed (with the 90% confidence intervals) $t_{1/2}$. t_{max} was compared using Wilcoxon signed-rank tests.

Sponsor: AFT Pharmaceuticals Ltd															
Generic Name Paracetamol and Ibuprofen		TABLE REFERENCE PART(S)													
(Treatment A) 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted		6. DISCUSSION AND CONCLUSION													
(Treatment B) 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted															
(Treatment C) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted															
(Treatment D) 2 tablets of Maxigesic® (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed															
CONFIDENCE INTERVALS (PARAMETRIC METHOD)		Confidence Intervals for t _{1/2} of Paracetamol for the un-transformed Treatments A and C Ratios of: t _{1/2} (C and A) (89.96-108.02) % Statistical evaluation of t _{max} obtained from paracetamol using non parametric Wilcoxon Matched Pairs test results after single dose administration of Treatments A and C.													
		<table><tr><td>t_{max} Treatment A (N=26)</td><td>t_{max} Treatment C (N=26)</td><td>T</td><td>Z</td><td>p-level</td></tr><tr><td>0.76</td><td>0.73</td><td>88.50000</td><td>5.123144</td><td>0.0000</td></tr></table>				t _{max} Treatment A (N=26)	t _{max} Treatment C (N=26)	T	Z	p-level	0.76	0.73	88.50000	5.123144	0.0000
		t _{max} Treatment A (N=26)	t _{max} Treatment C (N=26)	T	Z	p-level									
		0.76	0.73	88.50000	5.123144	0.0000									
Statistical evaluation of t _{max} obtained from paracetamol using non parametric Wilcoxon Matched Pairs test results after single dose administration of Treatments C and D.															
<table><tr><td>t_{max} Treatment C (N=26)</td><td>t_{max} Treatment D (N=26)</td><td>T</td><td>Z</td><td>p-level</td></tr><tr><td>0.73</td><td>1.15</td><td>150.5000</td><td>4.260896</td><td>0.0000</td></tr></table>				t _{max} Treatment C (N=26)	t _{max} Treatment D (N=26)	T	Z	p-level	0.73	1.15	150.5000	4.260896	0.0000		
t _{max} Treatment C (N=26)	t _{max} Treatment D (N=26)	T	Z	p-level											
0.73	1.15	150.5000	4.260896	0.0000											
		Confidence Intervals for Paracetamol for the log-transformed (Treatment D, Fed) / (Treatment C, Fasted) Ratios of: C _{max} 89.32 (76.37-104.47) % AUC _{0→t} 99.42 (95.89-103.08) % AUC _{0→∞} 100.78 (97.19-104.48) %													

CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Ibuprofen for the log-transformed (Treatment B) / (Treatment C) Ratios of: C_{max} 102.85 (90.21-117.26) % $AUC_{0 \rightarrow t}$ 98.83 (93.48-104.47) % $AUC_{0 \rightarrow \infty}$ 98.94 (93.98-104.16) % Confidence Intervals for Ibuprofen for the log-transformed (Treatment B, Fasted) / (Treatment D, Fed) Ratios of: C_{max} 108.31 (96.09-122.08) % $AUC_{0 \rightarrow t}$ 111.79 (106.63-117.20) % $AUC_{0 \rightarrow \infty}$ 111.93 (106.83-117.27) %																																															
	The pharmacokinetic parameters for C_{max}, $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ for paracetamol and ibuprofen were similar between the fixed dose combination and mono-components (Table 1). The back-transformed 90% confidence intervals for C_{max}, $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ ratios fell within the 80% to 125% acceptable bioequivalence range. <table><tr><th>Paracetamol</th><th>C_{max} (ng/ml)</th><th>$AUC_{0 \rightarrow t}$ (ng.h/ml)</th><th>$AUC_{0 \rightarrow \infty}$ (ng.h/ml)</th><th>T_{max} (hrs)</th><th>$t_{1/2}$ (hrs)</th></tr><tr><td>Treatment A (fast)</td><td>14873.912</td><td>36508.6</td><td>38422</td><td>0.76</td><td>3.11</td></tr><tr><td>Treatment C (fast)</td><td>13894.909</td><td>38321.3</td><td>40465.5</td><td>0.73</td><td>3.14</td></tr><tr><td>Treatment D (fed)</td><td>12939.875</td><td>38111.3</td><td>40800.4</td><td>1.15</td><td>3.47</td></tr><tr><td colspan="6">Ibuprofen</td></tr><tr><td>Treatment B (fast)</td><td>22081.471</td><td>78563.9</td><td>80842.2</td><td>1.39</td><td>2.29</td></tr><tr><td>Treatment C (fast)</td><td>21481.832</td><td>80116.9</td><td>82298.4</td><td>1.6</td><td>2.12</td></tr><tr><td>Treatment D (fed)</td><td>20392.712</td><td>70247.6</td><td>72196.8</td><td>1.3</td><td>2.08</td></tr></table> <i>Table 1 Mean pharmacokinetic parameters of paracetamol and ibuprofen after administration of 1000 mg paracetamol (treatment A), 300 mg ibuprofen (treatment B) and of the combination 1000 mg paracetamol + 300 mg ibuprofen (treatments C and D) in fast and fed conditions.</i> The rate of absorption of was significantly prolonged for paracetamol and slightly delayed for ibuprofen when the fixed dose combination tablet was administered following a standard meal (treatment D) compared with when it was administered to participants in fasted state (treatment C). This delay was associated with a reduced C_{max} for both paracetamol and ibuprofen when the combination tablet was administered in the fed state (treatment D); the back-transformed 90% confidence intervals for the C_{max} for paracetamol being outside of the bioequivalence acceptance range of 80% to 125%. Additionally, in the fed state, the extent of absorption, as indicated by $AUC_{0 \rightarrow t}$ of both paracetamol and ibuprofen from the fixed dose combination tablet was slightly less compared with the fasted state, although the back transformed 90% CI for the $AUC_{0 \rightarrow t}$, along with $AUC_{0 \rightarrow \infty}$ fell within the bioequivalence acceptance range.	Paracetamol	C_{max} (ng/ml)	$AUC_{0 \rightarrow t}$ (ng.h/ml)	$AUC_{0 \rightarrow \infty}$ (ng.h/ml)	T_{max} (hrs)	$t_{1/2}$ (hrs)	Treatment A (fast)	14873.912	36508.6	38422	0.76	3.11	Treatment C (fast)	13894.909	38321.3	40465.5	0.73	3.14	Treatment D (fed)	12939.875	38111.3	40800.4	1.15	3.47	Ibuprofen						Treatment B (fast)	22081.471	78563.9	80842.2	1.39	2.29	Treatment C (fast)	21481.832	80116.9	82298.4	1.6	2.12	Treatment D (fed)	20392.712	70247.6	72196.8	1.3
Paracetamol	C_{max} (ng/ml)	$AUC_{0 \rightarrow t}$ (ng.h/ml)	$AUC_{0 \rightarrow \infty}$ (ng.h/ml)	T_{max} (hrs)	$t_{1/2}$ (hrs)																																											
Treatment A (fast)	14873.912	36508.6	38422	0.76	3.11																																											
Treatment C (fast)	13894.909	38321.3	40465.5	0.73	3.14																																											
Treatment D (fed)	12939.875	38111.3	40800.4	1.15	3.47																																											
Ibuprofen																																																
Treatment B (fast)	22081.471	78563.9	80842.2	1.39	2.29																																											
Treatment C (fast)	21481.832	80116.9	82298.4	1.6	2.12																																											
Treatment D (fed)	20392.712	70247.6	72196.8	1.3	2.08																																											
CONCLUSIONS																																																



Paracetamol (plot A) mean plasma concentrations after single dose administration of Treatments A, C and D, Ibuprofen (plot B) mean plasma concentrations after single dose administration of Treatments B, C and D to 26 healthy subjects.

Final Issuance Date

13/04/14

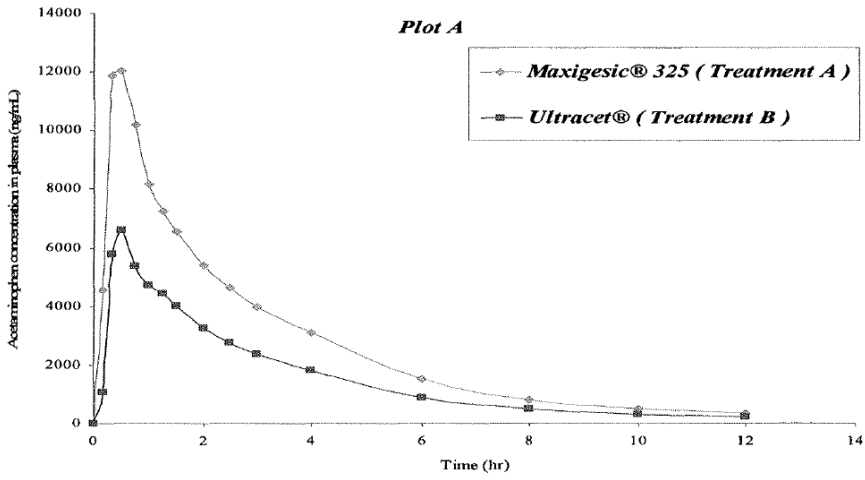
4.2.4 Study AFT-MX-13a (Comparative BA with List Drug Products Fasting)

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Acetaminophen and Ibuprofen	TABLE REFERENCE PART (S) 1. ETHICS 2. INTRODUCTION 3. INVESTIGATION
(Treatment A) Three tablets of <i>Maxigesic</i> [®] 325 (total dose acetaminophen 975 mg + ibuprofen 292.5 mg)	
(Treatment B) Two tablets of <i>Ultracet</i> [®] (total dose acetaminophen 650 mg + tramadol HCl 75 mg).	
(Treatment C) One tablet of <i>Ibuprofen</i> (each tablet containing 800 mg ibuprofen)	
STUDY TITLE	Randomized, Single Dose, Three-Period, Cross-Over Open-Label Study To Evaluate and Compare The Pharmacokinetic Parameters Of AFT Pharmaceuticals Ltd. Test Product <i>Maxigesic</i> [®] 325 (325 mg Acetaminophen And 97.5 mg Ibuprofen Per Film Coated Tablet (Treatment A)) Relative To Janssen Pharmaceuticals, Inc. <i>Ultracet</i> [®] (325 mg Acetaminophen And 37.5 mg Tramadol Hydrochloride Per Film Coated Tablet (Treatment B)) And Dr. Reddy's Laboratories LA LLC <i>Ibuprofen</i> (800 mg Ibuprofen Per Film Coated Tablet (Treatment C)), In 30 Healthy Adults Under Fasting Conditions.
IPRC PROTOCOL CODE NO.	ACIB-T004
IPRC STUDY CODE	ACIB-AFT-T0116/1202
INSTITUTIONAL REVIEW BOARD	Institutional Review Board of IPRC, Jordan.
INVESTIGATORS	Study Director: Naji Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, International Pharmaceutical Research Center, Jordan. Principal Investigator: Isam Salem, B.Sc. Chem., B.Sc. Pharm., Ph.D. International Pharmaceutical Research Center, Jordan. Study Physician (Co-Investigator): Usama Harb, M.D., International Pharmaceutical Research Center, Jordan. Co-Investigator: Ahmad Atiyeh, M.D., International Pharmaceutical Research Center, Jordan.
STUDY CENTRE	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan.

SPONSOR: AFT Pharmaceuticals Ltd

Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
STUDY PERIODS	Screening: 27/03/16 Enrolment: 01/04/16 Dosing Period I: 02/04/16 First Sample Collected: 02/04/16 Dosing Period II: 05/04/16 Dosing Period III: 08/04/16 Last sample Collected: 08/04/16
PHASE OF DEVELOPMENT	Phase I – Pharmacokinetic Confirmatory Study
OBJECTIVES	Primary Objectives: - To determine and compare dose-normalized acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, T_{max}, K_{el} and $t_{1/2}$) between <i>Maxigesic</i>[®] 325 (AFT Pharmaceuticals Ltd) and <i>Ultracet</i>[®] (Janssen Pharmaceuticals, Inc.) and <i>ibuprofen</i> (Dr. Reddy's Laboratories LA LLC) under fasting conditions. Secondary Objective: - To compare the safety and tolerability of <i>Maxigesic</i>[®] 325 (AFT Pharmaceuticals Ltd) with that of <i>Ultracet</i>[®] (Janssen Pharmaceuticals, Inc.) and <i>ibuprofen</i> (Dr. Reddy's Laboratories LA LLC) under fasting conditions.
CLINICAL LABORATORY	IPRC clinical laboratory
ANALYTICAL SITE	(b) (4)
BIOANALYTICAL METHODOLOGY	LC/MS/MS Detector with LLOQ = 50.000 ng/ml for Acetaminophen and Ibuprofen.
STUDY SUBJECTS	The study protocol called for 30 healthy subjects, 30 subjects were dosed and completed the crossover.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male subjects with the age range between 18 and 50 years, with the body mass index (BMI) between 18.5 and 30.0 kg/m ² , having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria.
DOSAGE REGIMEN	(Treatment A): Single-Dose, Three tablets of <i>Maxigesic</i> [®] 325 (total dose acetaminophen 975 mg + ibuprofen 292.5 mg). Batch No. BAD5401, Expiry Date: 10/17. (Treatment B): Single-Dose, Two tablets of <i>Ultracet</i> [®] (total dose acetaminophen 650 mg + tramadol HCl 75 mg). Batch No. 15AG829, Expiry Date: 11/17. (Treatment C): One tablet of <i>Ibuprofen</i> (each tablet containing 800 mg ibuprofen). Batch No. L300415, Expiry Date: 07/17.

SPONSOR: AFT Pharmaceuticals Ltd													
Generic Name	TABLE REFERENCE PART(S)												
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS (CONTINUED)												
ADMISSION AND CONFINEMENT	Subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, and confined until 12-hour sample was collected.												
DRUG ADMINISTRATION	Each subject received an oral dose of the assigned treatment, according to a randomization scheme, administered with 240 ml water.												
WASHOUT PERIOD	Three-days between each two consecutive study drug administration.												
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory tests, ECG, physical examination and vital signs.												
BLOOD SAMPLING SCHEDULE	Sixteen blood samples were drawn at 0.00 (one pre-dose sample), and at 10, 20, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00 and 12.00 hours (post-dose) in each period. The total volume of blood draws did not exceed 450 ml.												
BLOOD SAMPLES HANDLING	The blood samples for acetaminophen and Ibuprofen were collected in lithium heparinized tubes, centrifuged and the resulting plasma samples were immediately stored.												
CLINICAL SAMPLES STORAGE	Plasma samples were stored under a nominal temperature of -70°C until analyzed.												
SAFETY AND TOLERABILITY	All treatments were safe and well tolerated.												
PHARMACOKINETIC PARAMETERS	C_{max} , $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, t_{max} , K_{el} and $t_{1/2}$												
STATISTICAL METHODS	The assessment of the relative bioavailability is based upon 90% confidence intervals for the ratio of dose-normalized (i.e. acetaminophen – scale <i>Maxigeisic</i> [®] 325 by 66.667% to be similar to <i>Ultracet</i> [®] dose and Ibuprofen – scale <i>Ibuprofen</i> 800 mg by 36.563% to be similar to <i>Maxigesic</i> [®] 325 dose) geometric means (test/reference) for C_{max} , $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of acetaminophen and ibuprofen.												
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Acetaminophen for the log-transformed Test product (Treatment A) / Reference product (Treatment B) Ratios of: <table> <tr> <td>C_{max}</td> <td>129.25 (113.42-147.30) %</td> </tr> <tr> <td>$AUC_{0 \rightarrow t}$</td> <td>115.58 (111.68-119.62) %</td> </tr> <tr> <td>$AUC_{0 \rightarrow \infty}$</td> <td>114.57 (110.74-118.54) %</td> </tr> </table> Confidence Intervals for Ibuprofen for the log-transformed Test product (Treatment A) / Reference product (Treatment C) Ratios of: <table> <tr> <td>C_{max}</td> <td>118.70 (110.41-127.62) %</td> </tr> <tr> <td>$AUC_{0 \rightarrow t}$</td> <td>115.02 (110.73-119.47) %</td> </tr> <tr> <td>$AUC_{0 \rightarrow \infty}$</td> <td>115.03 (110.82-119.41) %</td> </tr> </table>	C_{max}	129.25 (113.42-147.30) %	$AUC_{0 \rightarrow t}$	115.58 (111.68-119.62) %	$AUC_{0 \rightarrow \infty}$	114.57 (110.74-118.54) %	C_{max}	118.70 (110.41-127.62) %	$AUC_{0 \rightarrow t}$	115.02 (110.73-119.47) %	$AUC_{0 \rightarrow \infty}$	115.03 (110.82-119.41) %
C_{max}	129.25 (113.42-147.30) %												
$AUC_{0 \rightarrow t}$	115.58 (111.68-119.62) %												
$AUC_{0 \rightarrow \infty}$	114.57 (110.74-118.54) %												
C_{max}	118.70 (110.41-127.62) %												
$AUC_{0 \rightarrow t}$	115.02 (110.73-119.47) %												
$AUC_{0 \rightarrow \infty}$	115.03 (110.82-119.41) %												

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONCLUSIONS	The dose-normalized acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$) were compared between the three different treatments <i>Maxigesic</i>[®] 325 (AFT Pharmaceuticals Ltd) and <i>Ultracet</i>[®] (Janssen Pharmaceuticals, Inc.) and <i>Ibuprofen</i> (Dr. Reddy's Laboratories LA LLC) under fasting conditions and it was found that both dose normalized $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ limits fell within the 80-125% bioequivalence range, except for dose normalized limits of C_{max}. For C_{max} the point estimate and upper limit of the 90% CI for acetaminophen were higher for <i>Maxigesic</i>[®] 325 than <i>Ultracet</i>[®]. The point estimate for Ibuprofen was within the 80-125% bioequivalence range, but the upper limit of 90% CI for ibuprofen was slightly higher and did not fall within the normal range of 80-125%. Despite of the slight differences in the rate of absorption the exposure to <i>Maxigesic</i>[®] 325 was found to be similar to that of <i>Ultracet</i>[®] and <i>Ibuprofen</i> (Dr. Reddy's Laboratories).
 Plot A Acetaminophen concentration in plasma (ng/mL) Time (hr) —◆— <i>Maxigesic</i>[®] 325 (Treatment A) —■— <i>Ultracet</i>[®] (Treatment B)	

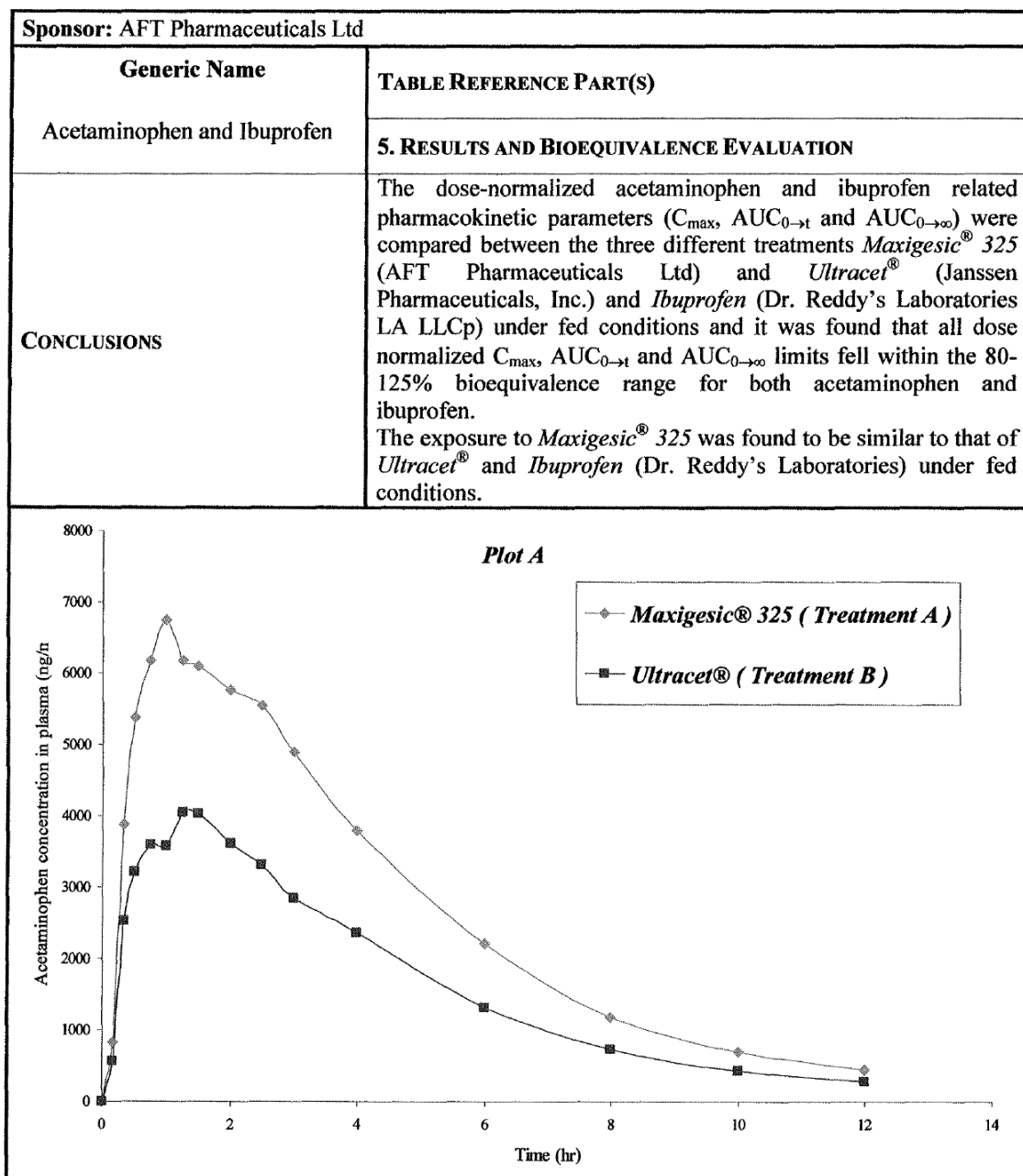
Sponsor: AFT Pharmaceuticals Ltd																																		
Generic Name	TABLE REFERENCE PART(S)																																	
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION																																	
Plot B <table><caption>Estimated data for Plot B: Ibuprofen concentration (ng/mL) vs Time (hr)</caption><thead><tr><th>Time (hr)</th><th>Maxigesic® 325 (Treatment A) (ng/mL)</th><th>Ibuprofen (Treatment C) (ng/mL)</th></tr></thead><tbody><tr><td>0</td><td>0</td><td>0</td></tr><tr><td>0.5</td><td>10,000</td><td>25,000</td></tr><tr><td>1</td><td>17,000</td><td>37,000</td></tr><tr><td>2</td><td>13,000</td><td>30,000</td></tr><tr><td>3</td><td>11,000</td><td>25,000</td></tr><tr><td>4</td><td>8,000</td><td>20,000</td></tr><tr><td>6</td><td>4,000</td><td>10,000</td></tr><tr><td>8</td><td>2,000</td><td>5,000</td></tr><tr><td>10</td><td>1,000</td><td>2,000</td></tr><tr><td>12</td><td>500</td><td>1,000</td></tr></tbody></table> Acetaminophen (plot A) mean plasma concentration after single dose administration of Treatments A and B to 30 healthy subjects and Ibuprofen (plot B) mean plasma concentration after single dose administration of Treatment A and C to 30 healthy subjects.		Time (hr)	Maxigesic® 325 (Treatment A) (ng/mL)	Ibuprofen (Treatment C) (ng/mL)	0	0	0	0.5	10,000	25,000	1	17,000	37,000	2	13,000	30,000	3	11,000	25,000	4	8,000	20,000	6	4,000	10,000	8	2,000	5,000	10	1,000	2,000	12	500	1,000
Time (hr)	Maxigesic® 325 (Treatment A) (ng/mL)	Ibuprofen (Treatment C) (ng/mL)																																
0	0	0																																
0.5	10,000	25,000																																
1	17,000	37,000																																
2	13,000	30,000																																
3	11,000	25,000																																
4	8,000	20,000																																
6	4,000	10,000																																
8	2,000	5,000																																
10	1,000	2,000																																
12	500	1,000																																
Final Report Date	13 July 2016																																	

4.2.5 Study AFT-MX-13b (Comparative BA with List Drug Products Fed)

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Acetaminophen and Ibuprofen	TABLE REFERENCE PART (S)
(Treatment A) Three tablets of <i>Maxigesic</i> [®] 325 (total dose acetaminophen 975 mg + ibuprofen 292.5 mg)	
(Treatment B) Two tablets of <i>Ultracet</i> [®] (total dose acetaminophen 650 mg + tramadol HCl 75 mg).	
(Treatment C) One tablet of <i>Ibuprofen</i> (each tablet containing 800 mg ibuprofen)	
STUDY TITLE	Randomized, Single Dose, Three-Period, Cross-Over Open-Label Study To Evaluate and Compare The Pharmacokinetic Parameters Of AFT Pharmaceuticals Ltd. Test Product <i>Maxigesic</i> [®] 325 (325 mg Acetaminophen And 97.5 mg Ibuprofen Per Film Coated Tablet (Treatment A)) Relative To Janssen Pharmaceuticals, Inc. <i>Ultracet</i> [®] (325 mg Acetaminophen And 37.5 mg Tramadol Hydrochloride Per Film Coated Tablet (Treatment B)) And Dr. Reddy's Laboratories LA LLC <i>Ibuprofen</i> (800 mg Ibuprofen Per Film Coated Tablet (Treatment C)), In 30 Healthy Adults Under Fed Conditions.
IPRC PROTOCOL CODE NO.	ACIB-T005
IPRC STUDY CODE	ACIB-AFT-T0116/1203
INSTITUTIONAL REVIEW BOARD	Institutional Review Board of IPRC, Jordan.
INVESTIGATORS	Study Director: Naji Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, International Pharmaceutical Research Center, Jordan. Principal Investigator: Isam Salem, B.Sc. Chem., B.Sc. Pharm., Ph.D. International Pharmaceutical Research Center, Jordan. Study Physician (Co-Investigator): Usama Harb, M.D., International Pharmaceutical Research Center, Jordan. Co-Investigator: Ahmad Atiyeh, M.D., International Pharmaceutical Research Center, Jordan.
STUDY CENTRE	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan.

SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
STUDY PERIODS	Screening: 27/03/16 Enrolment: 01/04/16 Dosing Period I: 02/04/16 First Sample Collected: 02/04/16 Dosing Period II: 05/04/16 Dosing Period III: 08/04/16 Last sample Collected: 08/04/16
PHASE OF DEVELOPMENT	Phase I – Dose-Normalized Pharmacokinetic Study
OBJECTIVES	Primary Objectives: - To determine and compare dose-normalized acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, T_{max}, K_{el} and $t_{1/2}$) between <i>Maxigesic</i>[®] 325 (AFT Pharmaceuticals Ltd) and <i>Ultracet</i>[®] (Janssen Pharmaceuticals, Inc.) and <i>ibuprofen</i> (Dr. Reddy's Laboratories LA LLC) under fed conditions. Secondary Objective: - To compare the safety and tolerability of <i>Maxigesic</i>[®] 325 (AFT Pharmaceuticals Ltd) with that of <i>Ultracet</i>[®] (Janssen Pharmaceuticals, Inc.) and <i>ibuprofen</i> (Dr. Reddy's Laboratories LA LLC) under fed conditions.
CLINICAL LABORATORY	IPRC clinical laboratory
ANALYTICAL SITE	(b) (4)
BIOANALYTICAL METHODOLOGY	LC/MS/MS Detector with LLOQ = 50.000 ng/ml for Acetaminophen and Ibuprofen.
STUDY SUBJECTS	The study protocol called for 30 healthy subjects, 30 subjects were dosed and 29 subjects completed the crossover.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male subjects with the age range between 18 and 50 years, with the body mass index (BMI) between 18.5 and 30.0 kg/m ² , having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria.
DOSAGE REGIMEN	(Treatment A): Single-Dose, Three tablets of <i>Maxigesic</i>[®] 325 (total dose acetaminophen 975 mg + ibuprofen 292.5 mg). Batch No. BAD5401, Expiry Date: 10/17. (Treatment B): Single-Dose, Two tablets of <i>Ultracet</i>[®] (total dose acetaminophen 650 mg + tramadol HCl 75 mg). Batch No. 15AG829, Expiry Date: 11/17. (Treatment C): One tablet of <i>Ibuprofen</i> (each tablet containing 800 mg ibuprofen). Batch No. L300415, Expiry Date: 07/17.

SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS (CONTINUED)
ADMISSION AND CONFINEMENT	Subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, then received a standardized breakfast served 30 minutes prior to study drug administration and confined until 12-hour sample was collected.
DRUG ADMINISTRATION	Each subject received an oral dose of the assigned treatment, according to a randomization scheme, administered with 240 ml water after a standardized breakfast served 30 minutes prior to study drug administration.
WASHOUT PERIOD	Three-days between each two consecutive study drug administration.
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory tests, ECG, physical examination and vital signs.
BLOOD SAMPLING SCHEDULE	Sixteen blood samples were drawn at 0.00 (one pre-dose sample), and at 10, 20, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00 and 12.00 hours (post-dose) in each period. The total volume of blood draws did not exceed 450 ml.
BLOOD SAMPLES HANDLING	The blood samples for acetaminophen and ibuprofen were collected in lithium heparinized tubes, centrifuged and the resulting plasma samples were immediately stored.
CLINICAL SAMPLES STORAGE	Plasma samples were stored under a nominal temperature of -70°C until analyzed.
SAFETY AND TOLERABILITY	All treatments were safe and well tolerated.
PHARMACOKINETIC PARAMETERS	C_{max} , $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, t_{max} , K_{el} and $t_{1/2}$
STATISTICAL METHODS	The assessment of the relative bioavailability is based upon 90% confidence intervals for the ratio of dose-normalized (i.e. acetaminophen – scale <i>Maxigeisic</i> ® 325 by 66.667% to be similar to <i>Ultracet</i> ® dose and Ibuprofen – scale <i>Ibuprofen</i> 800 mg by 36.563% to be similar to <i>Maxigesic</i> ® 325 dose) geometric means (test/reference) for C_{max} , $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of acetaminophen and ibuprofen.
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Acetaminophen for the log-transformed Test product (Treatment A) / Reference product (Treatment B) Ratios of: C_{max} 103.77 (91.93-117.13) % $AUC_{0 \rightarrow t}$ 109.31 (107.12-111.55) % $AUC_{0 \rightarrow \infty}$ 108.99 (106.89-111.13) % Confidence Intervals for Ibuprofen for the log-transformed Test product (Treatment A) / Reference product (Treatment C) Ratios of: C_{max} 104.05 (93.91-115.29) % $AUC_{0 \rightarrow t}$ 114.20 (110.44-118.09) % $AUC_{0 \rightarrow \infty}$ 113.33 (109.68-117.09) %



Sponsor: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION

Plot B

Ibuprofen concentration in plasma (ng/r)

Time (hr)

Maxigesic® 325 (Treatment A)

Ibuprofen (Treatment C)

Time (hr)	Maxigesic® 325 (Treatment A) (ng/r)	Ibuprofen (Treatment C) (ng/r)
0	0	0
0.5	4500	13500
1	10000	24500
1.5	11500	28500
2	11000	24500
3	10000	21000
4	8000	19000
6	5000	12500
8	3000	6000
10	2000	4000
12	1500	3000

Acetaminophen (plot A) mean plasma concentration after single dose administration of Treatments A and B to 29 healthy subjects and Ibuprofen (plot B) mean plasma concentration after single dose administration of Treatment A and C to 29 healthy subjects.

Final Report Date	07 August 2016
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4.2.6 Study AFT-MX-14a (Comparative BA FDC 325/97.5 Tablet vs FDC 500/150 Tablet, Suspension, and Sachet, Fasting)

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Acetaminophen and Ibuprofen	TABLE REFERENCE PART (S) 1. ETHICS 2. INTRODUCTION 3. INVESTIGATION
(Treatment A) Maxigesic® Oral Suspension (1000 mg acetaminophen + 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL])	
(Treatment B) Maxigesic® Sachet (1000 mg acetaminophen + 300 mg ibuprofen)	
(Treatment C) Maxigesic®, 2 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen)	
(Treatment D) Maxigesic® 325, 3 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen)	
STUDY TITLE	A Single Dose, Four-Way, Open-Label Study To Determine The Bioavailability Of Maxigesic® Oral Suspension, Maxigesic® Sachets, Maxigesic®, Maxigesic® 325, After Oral Administration In 28 Healthy Adult Volunteers Under Fasting Conditions.
IPRC PROTOCOL CODE NO.	ACIB-SLT006
IPRC STUDY CODE	ACIB-AFT-SLT0216/1227
INSTITUTIONAL REVIEW BOARD	Institutional Review Board of IPRC, Jordan.
INVESTIGATORS	Study Director: Naji Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, International Pharmaceutical Research Center, Jordan. Principal Investigator: Dr. Majdi Abu Awida, M.D., International Pharmaceutical Research Center, Jordan. Study Physician (Co-Investigator): Usama Harb, M.D., International Pharmaceutical Research Center, Jordan.
STUDY CENTRE	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan.

SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
STUDY PERIODS	Screening: 14/07/16 Dosing Period II: 29/07/16 Enrolment: 25/07/16 Dosing Period III: 01/08/16 Dosing Period I: 26/07/16 Dosing Period IV: 04/08/16 First Sample Collected: 26/07/16 Last sample Collected: 04/08/16
PHASE OF DEVELOPMENT	Phase I –Pharmacokinetic Study
OBJECTIVES	Primary Objectives: - To determine the pharmacokinetics parameters (C_{max}, $AUC_{0 \rightarrow 4}$, $AUC_{0 \rightarrow \infty}$, T_{max}, K_{el}, and $t_{1/2el}$) of acetaminophen and ibuprofen and compare them between the four groups. Secondary Objective: - To compare the safety and tolerability of all treatment groups.
CLINICAL LABORATORY	IPRC clinical laboratory
ANALYTICAL SITE	(b) (4)
BIOANALYTICAL METHODOLOGY	LC/MS/MS Detector with LLOQ = 50.000 ng/ml for Acetaminophen and Ibuprofen.
STUDY SUBJECTS	The study protocol called for 28 healthy subjects, 28 subjects were dosed and 26 subjects completed the crossover.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male subjects with the age range between 18 and 50 years, with the body mass index (BMI) between 18.5 and 30.0 kg/m ² , having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria.
DOSAGE REGIMEN	Treatment A (Test 1): Maxigesic [®] Oral Suspension (1000 mg acetaminophen + 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]). Batch No. SP021877, Re-test Date: 06/17. Treatment B (Test 2): Maxigesic [®] Sachet (1000 mg acetaminophen + 300 mg ibuprofen). Batch No. 4742-S1-008, Re-test Date: 12/17. Treatment C (Reference): Maxigesic [®] , 2 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen). Batch No. MWGE4028A, Expiry Date: 11/17. Treatment D (Test 3): Maxigesic [®] 325, 3 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen). Batch No. BAD5401, Expiry Date: 10/17.

SPONSOR: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS (CONTINUED)
ADMISSION AND CONFINEMENT	Subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, and confined until 12-hour sample was collected.
DRUG ADMINISTRATION	Tablet Formulations: Two Maxigesic® or three Maxigesic® 325 tablets. Oral Suspension: Subjects consumed 31.25 mL of Maxigesic® Oral Suspension. Sachet Formulation: the content of the sachet was poured in a mug and subjects were allowed to drink the 240 ml solution.
WASHOUT PERIOD	Three-days between each two consecutive study drug administration.
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory tests, ECG, physical examination and vital signs.
BLOOD SAMPLING SCHEDULE	Fourteen blood samples were drawn at 0.00 (one pre-dose sample), and at 5, 15, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 3.00, 6.00, 8.00, 10.00 and 12.00 hours (post-dose) in each period. The total volume of blood draws did not exceed 420 ml.
BLOOD SAMPLES HANDLING	The blood samples for acetaminophen and Ibuprofen were collected in lithium heparinized tubes, centrifuged and the resulting plasma samples were immediately stored.
CLINICAL SAMPLES STORAGE	Plasma samples were stored under a nominal temperature of -70°C until analyzed.
SAFETY AND TOLERABILITY	All treatments were safe and well tolerated.
PHARMACOKINETIC PARAMETERS	C_{max} , $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, t_{max} , K_{el} and $t_{1/2}$
STATISTICAL METHODS	The relative bioavailability of acetaminophen and ibuprofen from Maxigesic® Sachet and Maxigesic® Oral Suspension versus that from Maxigesic® and Maxigesic® 325 tablets was evaluated and compared for C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$, as the geometric mean ratio and the 90% confidence interval calculated from the mean differences in the mean log transformed data for oral administrations.

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 115.03 (98.90-133.79) % $AUC_{0 \rightarrow t}$ 100.92 (97.82-104.11) % $AUC_{0 \rightarrow \infty}$ 100.38 (97.27-103.59) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 133.67 (114.92-155.47) % $AUC_{0 \rightarrow t}$ 110.39 (107.01-113.89) % $AUC_{0 \rightarrow \infty}$ 109.64 (106.25-113.14) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] 325 (Treatment D) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 118.84 (102.18-138.23) % $AUC_{0 \rightarrow t}$ 102.49 (99.35-105.73) % $AUC_{0 \rightarrow \infty}$ 102.92 (99.74-106.21) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 96.79 (83.21-112.57) % $AUC_{0 \rightarrow t}$ 98.46 (95.44-101.58) % $AUC_{0 \rightarrow \infty}$ 97.53 (94.51-100.64) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 112.47 (96.70-130.82) % $AUC_{0 \rightarrow t}$ 107.71 (104.41-111.12) % $AUC_{0 \rightarrow \infty}$ 106.53 (103.23-109.93) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] Sachet (Treatment B) Ratios of: C_{max} 86.05 (73.99-100.09) % $AUC_{0 \rightarrow t}$ 91.41 (88.61-94.31) % $AUC_{0 \rightarrow \infty}$ 91.55 (88.72-94.48) %

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 101.20 (91.04-112.50) % $AUC_{0 \rightarrow t}$ 97.82 (92.95-102.94) % $AUC_{0 \rightarrow \infty}$ 97.32 (92.76-102.10) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 144.08 (129.61-160.17) % $AUC_{0 \rightarrow t}$ 104.43 (99.23-109.90) % $AUC_{0 \rightarrow \infty}$ 103.22 (98.39-108.29) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] 325 (Treatment D) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 107.49 (96.69-119.49) % $AUC_{0 \rightarrow t}$ 99.43 (94.48-104.64) % $AUC_{0 \rightarrow \infty}$ 98.99 (94.35-103.85) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 94.15 (84.69-104.67) % $AUC_{0 \rightarrow t}$ 98.38 (93.49-103.53) % $AUC_{0 \rightarrow \infty}$ 98.31 (93.71-103.14) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 134.05 (120.58-149.02) % $AUC_{0 \rightarrow t}$ 105.03 (99.80-110.53) % $AUC_{0 \rightarrow \infty}$ 104.28 (99.40-109.40) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] Sachet (Treatment B) Ratios of: C_{max} 70.24 (63.18-78.08) % $AUC_{0 \rightarrow t}$ 93.67 (89.01-98.58) % $AUC_{0 \rightarrow \infty}$ 94.28 (89.86-98.91) %

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONCLUSIONS	Acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$) were compared between the four different treatments under fasting conditions and it was found that both $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$ limits fell within the 80-125% bioequivalence range for both acetaminophen and ibuprofen. This data reinforces the evidence of a similar extent of absorption between all four formulations. Limits of C_{max} for acetaminophen did not fall within the 80-125% bioequivalence range for all treatments comparisons except for Treatments A/D comparison. Limits of C_{max} for ibuprofen fell within the 80-125% bioequivalence range for Treatments A/C, Treatments D/C and Treatments A/D but not for Treatments B/C, Treatments B/D and Treatments A/B. However, the higher C_{max} observed for Treatment B is expected due to the specific formulation (hot drink) where all the ingredients are completely dissolved in the solution prior to oral administration and thus conferring a rapid absorption from the gastrointestinal tract.
Plot A Acetaminophen concentration in plasma (µg/mL) Time (hr) Legend: - Maxigesic® Oral Suspension (Treatment A) - Maxigesic® Sachet (Treatment B) - Maxigesic® (Treatment C) - Maxigesic® 325 (Treatment D)	

Sponsor: AFT Pharmaceuticals Ltd	
Generic Name Acetaminophen and Ibuprofen	TABLE REFERENCE PART(S)
	5. RESULTS AND BIOEQUIVALENCE EVALUATION
Plot B Ibuprofen concentration in plasma (ng/ml) Time (hr) <i>Maxigesic® Oral Suspension (Treatment A)</i> <i>Maxigesic® Sachet (Treatment B)</i> <i>Maxigesic® (Treatment C)</i> <i>Maxigesic® 325 (Treatment D)</i> Acetaminophen (plot A) mean plasma concentration after single dose administration of Treatments A, B, C and D to 26 healthy subjects and Ibuprofen (plot B) mean plasma concentration after single dose administration of Treatments A, B, C and D to 26 healthy subjects.	
Final Report Date	19 October 2016

4.2.7 Study AFT-MX-14b (Comparative BA FDC 325/97.5 Tablet vs FDC 500/150 Tablet, Suspension, and Sachet, Fed)

Sponsor: AFT Pharmaceuticals Ltd.	
Generic Name Acetaminophen and Ibuprofen	TABLE REFERENCE PART (S) 1. ETHICS 2. INTRODUCTION 3. INVESTIGATION
(Treatment A) Maxigesic® Oral Suspension (1000 mg acetaminophen + 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL])	
(Treatment B) Maxigesic® Sachet (1000 mg acetaminophen + 300 mg ibuprofen)	
(Treatment C) Maxigesic®, 2 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen)	
(Treatment D) Maxigesic® 325, 3 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen)	
STUDY TITLE	A Single Dose, Four-Way, Open-Label Study To Determine The Bioavailability Of Maxigesic® Oral Suspension, Maxigesic® Sachets, Maxigesic®, Maxigesic® 325, After Oral Administration In 28 Healthy Adult Volunteers Under Fed Conditions.
IPRC PROTOCOL CODE NO.	ACIB-SLT007
IPRC STUDY CODE	ACIB-AFT-SLT0216/1228
INSTITUTIONAL REVIEW BOARD	Institutional Review Board of IPRC, Jordan.
INVESTIGATORS	Study Director: Naji Najib, B.Sc. Pharm, Ph.D., Professor of Pharmaceutics, International Pharmaceutical Research Center, Jordan. Principal Investigator: Dr. Majdi Abu Awida, M.D., International Pharmaceutical Research Center, Jordan. Study Physician (Co-Investigator): Usama Harb, M.D., International Pharmaceutical Research Center, Jordan.
STUDY CENTRE	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan.

SPONSOR: AFT Pharmaceuticals Ltd.	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS
STUDY PERIODS	Screening: 17/07/16 Dosing Period II: 29/07/16 Enrolment: 25/07/16 Dosing Period III: 01/08/16 Dosing Period I: 26/07/16 Dosing Period IV: 04/08/16 First Sample Collected: 26/07/16 Last sample Collected: 04/08/16
PHASE OF DEVELOPMENT	Phase I –Pharmacokinetic Study
OBJECTIVES	Primary Objectives: - To determine the pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, T_{max}, K_{el}, and $t_{1/2el}$) of acetaminophen and ibuprofen and compare them between the four groups. Secondary Objective: - To compare the safety and tolerability of all treatment groups.
CLINICAL LABORATORY	IPRC clinical laboratory
ANALYTICAL SITE	(b) (4)
BIOANALYTICAL METHODOLOGY	LC/MS/MS Detector with LLOQ = 50.000 ng/ml for Acetaminophen and Ibuprofen.
STUDY SUBJECTS	The study protocol called for 28 healthy subjects, 28 subjects were dosed and completed the crossover.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male subjects with the age range between 18 and 50 years, with the body mass index (BMI) between 18.5 and 30.0 kg/m ² , having no significant diseases as determined by medical history, physical examination and laboratory tests, having negative HIV and hepatitis B & C test results and being able and willing to abstain from any food or beverages as defined in the detailed inclusion criteria.
DOSAGE REGIMEN	Treatment A (Test 1): Maxigesic [®] Oral Suspension (1000 mg acetaminophen + 300 mg ibuprofen in 31.25 mL [160 mg acetaminophen + 48 mg ibuprofen/5 mL]). Batch No. SP021877, Re-test Date: 06/17. Treatment B (Test 2): Maxigesic [®] Sachet (1000 mg acetaminophen + 300 mg ibuprofen). Batch No. 4742-S1-008, Re-test Date: 12/17. Treatment C (Reference): Maxigesic [®] , 2 tablets (total dose 1000 mg acetaminophen + 300 mg ibuprofen). Batch No. MWGE4028A, Expiry Date: 11/17. Treatment D (Test 3): Maxigesic [®] 325, 3 tablets (total dose 975 mg acetaminophen + 292.5 mg ibuprofen). Batch No. BAD5401, Expiry Date: 10/17.

SPONSOR: AFT Pharmaceuticals Ltd.	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	3. INVESTIGATION (CONTINUED) 4. STUDY SUBJECTS (CONTINUED)
ADMISSION AND CONFINEMENT	Subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, then received a standardized breakfast served 30 minutes prior to study drug administration and confined until 12-hour sample was collected.
DRUG ADMINISTRATION	Tablet Formulations: Two Maxigesic® or three Maxigesic® 325 tablets Oral Suspension: Subjects consumed 31.25 mL of Maxigesic® Oral Suspension. Sachet Formulation: the contents of the sachet were poured in a mug and subjects were allowed to drink the 240 ml solution.
WASHOUT PERIOD	Three-days between each consecutive study drug administration.
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory tests, ECG, physical examination and vital signs.
BLOOD SAMPLING SCHEDULE	Fourteen blood samples were drawn at 0.00 (one pre-dose sample), and at 5, 15, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 3.00, 6.00, 8.00, 10.00 and 12.00 hours (post-dose) in each period. The total volume of blood drawn did not exceed 420 ml.
BLOOD SAMPLES HANDLING	The blood samples for acetaminophen and ibuprofen were collected in lithium heparinized tubes, centrifuged and the resulting plasma samples were immediately stored.
CLINICAL SAMPLES STORAGE	Plasma samples were stored under a nominal temperature of -70°C until analyzed.
SAFETY AND TOLERABILITY	All treatments were safe and well tolerated.
PHARMACOKINETIC PARAMETERS	C_{max} , $AUC_{0 \rightarrow t}$, $AUC_{0 \rightarrow \infty}$, t_{max} , K_{el} and $t_{1/2}$
STATISTICAL METHODS	The relative bioavailability of acetaminophen and ibuprofen from Maxigesic® Sachet and Maxigesic® Oral Suspension versus that from Maxigesic® and Maxigesic® 325 tablets was evaluated and compared for C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$, as the geometric mean ratio and the 90% confidence interval calculated from the mean differences in the mean log transformed data for oral administrations.

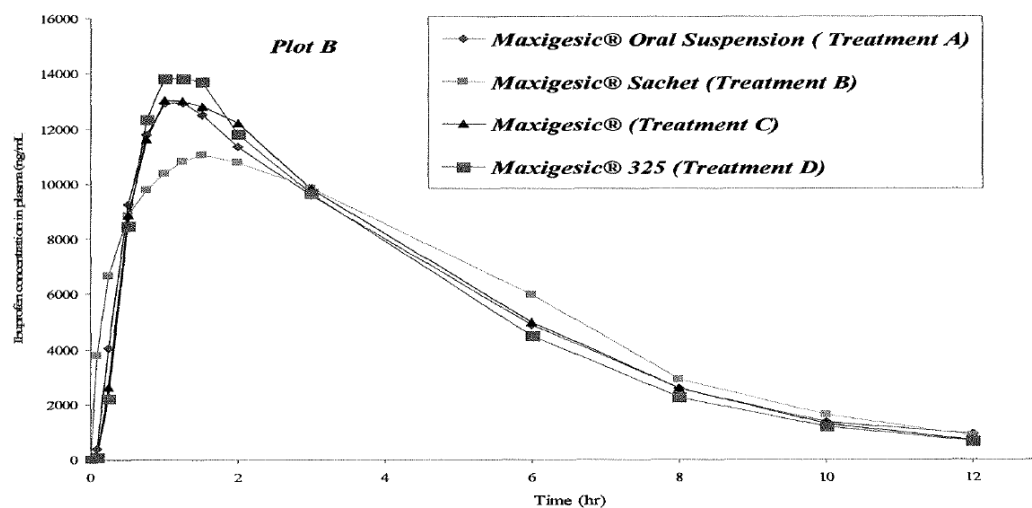
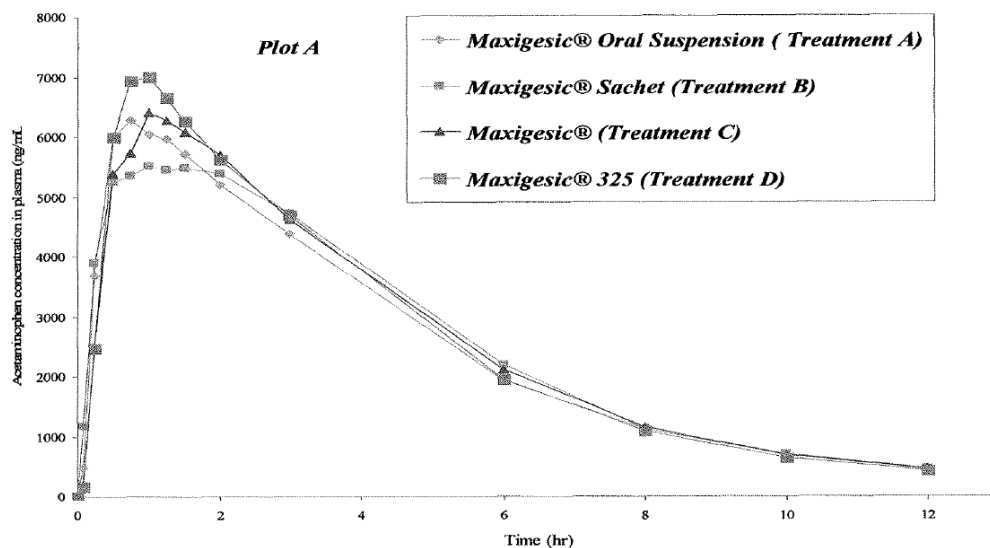
Sponsor: AFT Pharmaceuticals Ltd.	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 86.27 (73.64-101.07) % $AUC_{0 \rightarrow t}$ 97.33 (94.14-100.64) % $AUC_{0 \rightarrow \infty}$ 97.60 (94.52-100.77) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 77.25 (65.93-90.50) % $AUC_{0 \rightarrow t}$ 99.80 (96.52-103.19) % $AUC_{0 \rightarrow \infty}$ 99.85 (96.70-103.10) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] 325 (Treatment D) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 103.65 (88.47-121.43) % $AUC_{0 \rightarrow t}$ 100.33 (97.04-103.74) % $AUC_{0 \rightarrow \infty}$ 99.77 (96.63-103.02) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 83.24 (71.05-97.52) % $AUC_{0 \rightarrow t}$ 97.01 (93.83-100.30) % $AUC_{0 \rightarrow \infty}$ 97.82 (94.74-101.01) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 74.53 (63.61-87.32) % $AUC_{0 \rightarrow t}$ 99.47 (96.21-102.85) % $AUC_{0 \rightarrow \infty}$ 100.08 (96.93-103.33) %
	Confidence Intervals for Acetaminophen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] Sachet (Treatment B) Ratios of: C_{max} 111.68 (95.33-130.84) % $AUC_{0 \rightarrow t}$ 97.53 (94.33-100.84) % $AUC_{0 \rightarrow \infty}$ 97.75 (94.67-100.93) %

Sponsor: AFT Pharmaceuticals Ltd.	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 86.54 (77.19-97.02) % $AUC_{0 \rightarrow t}$ 99.41 (96.59-102.32) % $AUC_{0 \rightarrow \infty}$ 100.47 (97.52-103.52) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 75.31 (67.18-84.44) % $AUC_{0 \rightarrow t}$ 103.64 (100.69-106.67) % $AUC_{0 \rightarrow \infty}$ 104.62 (101.54-107.79) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] 325 (Treatment D) / Maxigesic [®] (Treatment C) Ratios of: C_{max} 101.41 (90.45-113.69) % $AUC_{0 \rightarrow t}$ 97.12 (94.36-99.97) % $AUC_{0 \rightarrow \infty}$ 97.17 (94.31-100.12) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 85.34 (76.12-95.67) % $AUC_{0 \rightarrow t}$ 102.36 (99.45-105.35) % $AUC_{0 \rightarrow \infty}$ 103.40 (100.36-106.54) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Sachet (Treatment B) / Maxigesic [®] 325 (Treatment D) Ratios of: C_{max} 74.27 (66.25-83.26) % $AUC_{0 \rightarrow t}$ 106.71 (103.68-109.83) % $AUC_{0 \rightarrow \infty}$ 107.67 (104.50-110.94) %
	Confidence Intervals for Ibuprofen for the log-transformed Maxigesic [®] Oral Suspension (Treatment A) / Maxigesic [®] Sachet (Treatment B) Ratios of: C_{max} 114.90 (102.49-128.82) % $AUC_{0 \rightarrow t}$ 95.92 (93.20-98.73) % $AUC_{0 \rightarrow \infty}$ 96.04 (93.21-98.95) %

Sponsor: AFT Pharmaceuticals Ltd.	
Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION
CONCLUSIONS	Acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{0 \rightarrow 1}$ and $AUC_{0 \rightarrow \infty}$) were compared between the four different treatments under fed conditions and it was found that both $AUC_{0 \rightarrow 1}$ and $AUC_{0 \rightarrow \infty}$ limits fell within the 80-125% bioequivalence range for both acetaminophen and ibuprofen. This data reinforces the evidence of a similar extent of absorption between all four formulations. Limits of C_{max} for both acetaminophen and ibuprofen did not fall within the 80-125% bioequivalence range for all treatments comparisons except for Maxigesic® 325 (Treatment D)/Maxigesic® (Treatment C) comparison. The effect of food on bioavailability is generally greatest when the drug product is administered shortly after a meal is ingested. In general, meals that are high in total calories and fat content are more likely to affect the gastrointestinal physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. A rough estimate of the effect of food on the pharmacokinetics of each of the products used in this study can be drawn by comparing the data from the current fed study with the data obtained from a similar study in fasted individuals (IPRC Study Code ACIB-AFT-SLT0216/1227). Overall, $AUC_{0 \rightarrow 1}$ and $AUC_{0 \rightarrow \infty}$ were not affected for either ingredient for any treatment, however a pronounced food effect on C_{max} for Maxigesic® Sachets and Maxigesic® Oral Suspension was observed. The food effects on C_{max} for these products could be due to the fact that both products are administered as solutions which probably made the effect of food more pronounced as the disintegration step is skipped.

Sponsor: AFT Pharmaceuticals Ltd.

Generic Name	TABLE REFERENCE PART(S)
Acetaminophen and Ibuprofen	5. RESULTS AND BIOEQUIVALENCE EVALUATION



Mean plasma concentrations of Acetaminophen (plot A) and Ibuprofen (plot B) after single dose administration of Treatments A, B, C and D to 28 healthy subjects.

Final Report Date	08 November 2016
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