CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	215320
Link to EDR	\\CDSESUB1\evsprod\NDA215320\0000
Submission Date	8/31/2021; PDUFA date: 6/30/2022
Submission Type	Standard Review; 505(b)(2) to Ultracet (acetaminophen 325 mg and tramadol HCl 37.5 mg) tablet (NDA 21123) and Motrin (ibuprofen) tablet (NDA 17463)
Brand Name	Combogesic IV
Generic Name	Acetaminophen 1000 mg/ibuprofen 300 mg in 100 mL injection
Dosage Form and Strength	Solution for injection
Route of Administration	IV infusion over 15 minutes
Proposed Indication	For the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. Combogesic IV is indicated for short-term use of five days or less.
Dosage Regimen	Acetaminophen 1000 mg/ibuprofen 300 mg administered as 15-min infusion every 6 hours, as necessary. Do not exceed a total daily dose of 4000 mg of acetaminophen from all sources
Applicant	AFT Pharmaceuticals, Inc.
Associated IND	IND 124213
OCP Reviewer	Wei Qiu
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 215320, for Combogesic IV (acetaminophen 1000 mg and ibuprofen 300 mg in 100 mL). This application was submitted as a 505(b)(2) on 8/31/2021. From clinical pharmacology perspective, the information submitted in this NDA is acceptable.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical pharmacology studies supported the dosing regimen used in the Phase 3 clinical trials.
General dosing instructions	Combogesic IV should be administered as a 15-minute intravenous infusion
Sponsor's Proposed Dosing in patient subgroups (intrinsic and extrinsic factors)	Not recommended in patients with renal impairment. Not recommended in patients with hepatic impairment

Labeling	Edits and comments are made on Highlights of Prescribing Information, Section 7 Drug Interaction, Section 8.6 Hepatic Impairment, Section 8.7 Renal Impairment, Section 12.2 Pharmacodynamics, and presentation of PK data in Section 12.3 Pharmacokinetics of the proposed labeling. See Section 2.4 of this review for more details.
Bridge between the to-be-marketed and clinical trial formulations	Combogesic IV product used in the clinical pharmacology and clinical studies are the final commercial product.
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

(1) Comparative Bioavailability of Combogesic IV in Comparison to Ultracet (NDA 21123) and IBU tablets (ANDA 75682): Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen, intravenous infusion over 15 minutes) exhibited 3.1-fold greater acetaminophen Cmax and 2-fold greater AUC0-t and AUC0-inf values than 2 x Ultracet tablets (acetaminophen 325 mg/37.5 mg tramadol per tablet). Combogesic IV exhibited similar ibuprofen Cmax and 55% lower ibuprofen AUC0-t and AUC0-inf values than 1 x IBU tablet (ibuprofen 800 mg per tablet), a generic product of Motrin (ibuprofen) tablet (NDA 017463).

The dose normalized Cmax values (Cmax/dose) of acetaminophen and ibuprofen for Combogesic IV were 2-fold and 2.4-fold greater than Ultracet and IBU, respectively. The dose normalized AUC0-t, and AUC0-inf values (AUC0-t/dose and AUC0-inf/dose) of acetaminophen for Combogesic IV were 30% and 28% greater than those for Ultracet. The dose normalized AUC0-t values of ibuprofen for Combogesic IV were 21% greater than those for IBU, while dose normalized AUC0-inf values of ibuprofen were comparable to that for IBU. The differences in dose normalized Cmax and AUC values were mainly due to routes of administration.

(2) Comparative Bioavailability of Combogesic IV in Comparison to FDC 500/150 Tablet (acetaminophen 500 mg/ibuprofen 150 mg) and Combogesic Tablet (acetaminophen 325 mg/ibuprofen 97.5 mg, review pending under NDA 209471 as date of May 23, 2022): Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen, intravenous infusion over 15 minutes) exhibited approximately 2-fold greater Cmax while similar AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to either 2 x FDC 500/150 tablets or 3 x Combogesic tablets. Both FDC 500/150 (acetaminophen 500 mg/ibuprofen 150 mg) tablet and Combogesic tablet (acetaminophen 325 mg/ibuprofen 97.5 mg) are developed by the same Sponsor of Combogesic IV.

(3) Dose Proportionality between Combogesic IV Full Dose vs Combogesic Half Dose: Acetaminophen and ibuprofen Cmax, AUC0-t and AUC0-inf values were dose proportional between Combogesic IV full dose and Combogesic IV half dose.

(4) No PK Drug Interaction between Intravenous Acetaminophen and Intravenous Ibuprofen in Combogesic IV: Acetaminophen and ibuprofen Cmax, AUC0-t and AUC0-inf values for Combogesic IV (acetaminophen 1000 mg and ibuprofen 300 mg) were bioequivalent to 1000 mg intravenous acetaminophen and 300 mg intravenous ibuprofen given alone, respectively.

- **Regulatory Background**

The Applicant has submitted NDA 215320 for Combogesic IV (aka Maxigesic IV) for the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary, as a 505(b)(2) submission, referencing Ultracet tablet (acetaminophen 325 mg and tramadol HCl 37.5 mg) (NDA 21123) and Motrin (ibuprofen) tablet (NDA 017463) as the listed drugs.

The applicant conducted Phase 3 Studies AFT-MXIV-07 and AFT-MXIV-11 with Combogesic IV. The Applicant stated that the primary support for the safety and efficacy of Combogesic IV is based on the results of the pivotal Phase 3 efficacy study AFT-MXIV-07 and safety data from AFT-MXIV-11. The pivotal Phase 3 study AFT-MXIV-07 was a randomized, double-blind, multiple-dose, parallel-group and placebo-controlled study to evaluate the safety and efficacy of Combogesic IV, intravenous acetaminophen and intravenous ibuprofen, and placebo administered every 6 hours for a total of 8 doses in subjects with acute postoperative pain after bunionectomy. Study AFT-MXIV-11 was an open-label and single arm study to determine the incidence of treatment-emergent adverse events, and changes in vital signs or clinical laboratory values associated with prolonged exposure to Combogesic IV. In addition, the applicant proposed to use the efficacy/safety data from FDC 500/150 tablets (acetaminophen 500 mg/ibuprofen 150 mg, aka Maxigesic tablets) and Combogesic tablets (acetaminophen 325 mg/ibuprofen 97.5 mg, aka FDC 325/97.5 or Maxigesic 325 tablets, review pending under NDA 209471 as date of May 23, 2022) as additional supportive information. Based on clinical review of NDA 209471, efficacy was established in the pivotal Phase 3 study AFT-MX-6 which was a randomized, double-blind, placebo-controlled, parallel-group, full factorial study evaluating the analgesic effect of Combogesic tablets in an acute dental pain population. The safety database was adequate to support the safety of acetaminophen and ibuprofen when used in combination, Combogesic tablets.

The clinical pharmacology program consisted of pharmacokinetic Studies AFT-MXIV-01, AFT-MXIV-06, and AFT-MXIV-12, and an in vitro drug interaction study. The Applicant conducted clinical pharmacology studies to evaluate the pharmacokinetics of Combogesic IV and establish the scientific bridge to the identified listed drug products, Ultracet tablet (acetaminophen 325 mg and tramadol HCl 37.5 mg) (NDA 21123) and Motrin (ibuprofen) tablet (NDA 017463). Because NDA 017463 product, Motrin tablet, was withdrawn not for reasons of safety or efficacy, a generic product Dr. Reddy's IBU tablet (ANDA 75682) to NDA 017463 was used as the comparator in the comparative bioavailability study (Study AFT-MXIV-12) to establish the scientific bridge to the listed drug product, Motrin. Study AFT-MXIV-01 compared the proposed Combogesic IV with FDC 500/150 tablets, Combogesic IV half dose, acetaminophen IV, and ibuprofen IV to evaluate comparative bioavailability to FDC 500/150 tablets, dose proportionality between Combogesic IV half dose and full dose, and PK drug interaction between intravenous acetaminophen and intravenous ibuprofen. Study AFT-MXIV-06 compared Combogesic IV with Ofirmev (IV acetaminophen), Caldolor (IV ibuprofen), and Combogesic tablets. At the pre-NDA

meeting, the sponsor informed the agency that they decided not to refer to Ofirmev and Caldolor as listed drugs for commercial reasons and proposed Ultracet and Motrin as listed drug products. An in vitro drug interaction study (CEREP human enzyme study) evaluating the effects of fixed combination of acetaminophen and ibuprofen on CYP1A, 2C9, 2C19, 2D6, 2E1, and 3A was previously submitted to NDA 209471 for Combogesic tablet and was reviewed under NDA 209471.

Submitted 3 Phase 1 comparative bioavailability studies are:

1. Study AFT-MXIV-01: Single-center, single-dose, open-label, randomized, five-way crossover study to evaluate the pharmacokinetic parameters of Maxigesic IV (intravenous paracetamol + intravenous ibuprofen), intravenous paracetamol, intravenous ibuprofen, and Maxigesic tablets, in healthy volunteers
2. Study AFT-MXIV-06: Single-center, single-dose, open-label, randomized, four-way crossover study to evaluate and compare the pharmacokinetic parameters of Maxigesic IV (intravenous acetaminophen + intravenous ibuprofen), Ofirmev (intravenous acetaminophen), Caldolor (intravenous ibuprofen), and Maxigesic 325 tablets, in healthy volunteers
3. Study AFT-MXIV-12: Randomized, Single Dose, Three-way Crossover Open Label Pharmacokinetic Parameters Study of AFT Pharmaceuticals LTD Maxigesic IV (1000 mg Acetaminophen + 300 mg Ibuprofen/100 mL Solution For Infusion), Infusion Over 15 minutes (One Dose Only), Janssen Pharmaceuticals, Inc. Ultracet (325 mg Acetaminophen + 37.5 mg Tramadol Hydrochloride Per Film Coated Tablet) Two Tablets and Dr. Reddy's Laboratories, Inc. IBU Ibuprofen Tablets, USP 800 mg (800 mg Ibuprofen per Film Coated Tablet) One Tablet, After an Oral Administration to 30 Healthy Adults Under Fasting Conditions

- **Summary of Pharmacokinetic Results**

(1). Comparative Bioavailability of Combogesic IV in Comparison to Ultracet (NDA 21123) and IBU (ANDA 75682) (Results from Study AFT-MXIV-12)

In support of the 505(b)(2) application, pharmacokinetic comparisons were made between the proposed Combogesic IV and listed drug Ultracet (acetaminophen 325 mg + tramadol HCl 37.5 mg per tablet, 2 tablets for a full dose) (NDA 21123) and IBU tablet (ibuprofen 800 mg per tablet, 1 tablet for a full dose) (ANDA 75682), a generic product to the listed drug Motrin in Study AFT-MXIV-12.

Study AFT-MXIV-12 was a single-dose, open-label, randomized, three-way crossover bioavailability study in healthy volunteers, which compared the Applicant's product, Combogesic IV (acetaminophen 1000 mg and ibuprofen 300 mg) given as 15-min intravenous infusion, with the reference products, 2 x Ultracet tablets (acetaminophen 325 mg and tramadol 37.5 mg per tablet) and 1 x IBU (ibuprofen 800 mg per tablet).

Median (min, max) Tmax values of acetaminophen and ibuprofen for Combogesic IV were at the end of 15-min intravenous infusion (i.e., 0.25 (0.17-0.33) h) and they were shorter than median (min, max) Tmax values of acetaminophen for Ultracet (i.e., 0.5 (0.33-2.0) h) and median (min, max) Tmax values of ibuprofen for IBU (i.e., 1.50 (0.75-4.0) h). The mean acetaminophen half-

life values for Combogesic IV and Ultracet were similar (e.g., 2.5 h for Combogesic IV and 2.7 h for Ultracet). Mean ibuprofen half-life values for Combogesic and IBU were similar (e.g., 2.2 h for Combogesic IV and 2.1 h for IBU) (**Tables 1** and **2**).

Table 1 Summary of Acetaminophen Plasma Pharmacokinetic Parameters for Combogesic IV and Ultracet (Study AFT-MXIV-12)

Pharmacokinetic Parameter	Treatment (Mean ± SD)	
	Combogesic IV: acetaminophen 1000 mg and ibuprofen 300 mg, 15 min IV infusion (N=29)	2 x Ultracet Tablets: acetaminophen 650 mg and 75 mg tramadol (N=29)
Cmax (ng/ml)	34304.699 ± 11865.89	11324.480 ± 4732.47
Cmax/Dose (ng/ml/mg dose)	34.305 ± 11.87	17.422 ± 7.28
AUC0-t (ng.h/ml)	54356.8 ± 16878.86	27414.5 ± 8720.33
AUC0-t/Dose (ng.h/ml/mg dose)	54.36 ± 16.88	42.18 ± 13.42
AUC0-t (ng.h/ml)	56476.4 ± 18127.52	28798.0 ± 9411.02
AUC0-inf/Dose (ng.h/ml/mg dose)	56.48 ± 18.13	44.30 ± 14.48
Tmax (h)*	0.25 (0.17 - 0.33)	0.50 (0.33 - 2.00)
Kel (1/h)	0.2886 ± 0.06	0.2785 ± 0.07
t1/2 (h)	2.50 ± 0.52	2.70 ± 1.02
AUC0-t /AUC0-inf (%)	96.58 ± 1.85	95.54 ± 2.44

*median (min-max)
(Source: 2.7.1 Summary of Biopharmaceutic Studies p 15/18)

Table 2 Summary of Ibuprofen Pharmacokinetic Parameters for Combogesic IV and IBU (Study AFT-MXIV-12)

Pharmacokinetic Parameter	Treatment (Mean ± SD)	
	Combogesic IV: acetaminophen 1000 mg and ibuprofen 300 mg, 15 min IV infusion (N=29)	1 x IBU Tablet: ibuprofen 800 mg (N=29)
Cmax (ng/ml)	48118.759 ± 8870.66	54124.990 ± 14538.08
Cmax/Dose (ng/ml/mg dose)	160.396 ± 29.57	67.656 ± 18.17
AUC0-t (ng.h/ml)	100042.3 ± 27288.90	221600.0 ± 76230.72
AUC0-t/Dose (ng.h/ml/mg dose)	333.47 ± 90.96	277.00 ± 95.29
AUC0-inf (ng.h/ml)	102820.6 ± 30630.98	230287.8 ± 91712.81
AUC0-inf/Dose (ng.h/ml/mg dose)	342.74 ± 102.10	287.86 ± 114.64
Tmax (h)*	0.25 (0.17 - 0.33)	1.50 (0.75 - 4.00)
Kel (1/h)	0.3207 ± 0.05	0.3441 ± 0.07

t1/2 (h)	2.22 ± 0.39	2.10 ± 0.52
AUC0-t /AUC0-inf (%)	97.68 ± 1.63	97.11 ± 2.71

*median (min-max)
(Source: 2.7.1 Summary of Biopharmaceutic Studies p 15/18)

Combogesic IV exhibited 3.1-fold greater acetaminophen Cmax and 2-fold greater acetaminophen AUC0-t and AUC0-inf values than 2 x Ultracet tablets; Combogesic IV exhibited similar ibuprofen Cmax and 55% lower AUC0-t and AUC0-inf values than 1 x IBU tablet. The dose normalized Cmax, AUC0-t, and AUC0-inf values of acetaminophen (Cmax/dose, AUC0-t/dose and AUC0-inf/dose) for Combogesic IV were 2-fold, 30%, and 28% greater than those for Ultracet. The dose normalized Cmax and AUC0-t of ibuprofen for Combogesic IV were 2.4-fold and 21% greater than those for IBU, while dose normalized AUC0-inf of ibuprofen were comparable to that for IBU because the 90% confidence intervals for the geometric mean ratios fell within the 80 to 125% bioequivalence range. (**Tables 3** and **4**). Overall, the 2 to 2.4-fold greater Cmax/dose of acetaminophen and ibuprofen for Combogesic IV were due to differences in routes of administrations. Combogesic IV showed slightly greater AUC values than Ultracet and IBU (e.g., 28% greater AUC0-inf/dose of acetaminophen; comparable AUC0-inf/dose of ibuprofen).

Table 3 Statistical Assessment of Acetaminophen PK Parameters (Combogesic IV/Ultracet)

Parameter	90% Confidence interval			Intrasubject CV%
	Point estimate %	Lower Limit %	Upper Limit %	
Cmax	310.27	270.74	355.58	31.10
Cmax/Dose	201.68	175.98	231.12	
AUC0-t	199.42	191.87	207.27	8.63
AUC0-t/Dose	129.62	124.71	134.73	
AUC0-inf	197.27	189.60	205.25	8.86
AUC0-inf/Dose	128.22	123.24	133.41	

(Source: 2.7.1 Summary of Biopharmaceutic Studies p16/18)

Table 4 Statistical Assessment of Ibuprofen PK Parameters (Combogesic IV/IBU)

Parameter	90% Confidence interval			Intrasubject CV%
	Point estimate %	Lower Limit %	Upper Limit %	
Cmax	90.47	84.80	96.51	14.49
Cmax/Dose	241.25	226.14	257.36	
AUC0-t	45.55	44.07	47.09	7.42
AUC0-t/Dose	121.48	117.51	125.58	
AUC0-inf	45.27	43.74	46.86	7.67
AUC0-inf/Dose	120.73	116.65	124.95	

(Source: 2.7.1 Summary of Biopharmaceutic Studies p16/18)

(2). Comparative Bioavailability of Combogesic IV in Comparison to FDC 500/150 Tablets (Results from Study AFT-MXIV-01) or Combogesic Tablets (aka FDC 325/97.5 Tablets) (Results from Study AFT-MXIV-06)

The PK of the proposed Combogesic IV were compared with oral formulations, FDC 500/150 tablets and Combogesic tablets in Studies AFT-MXIV-01 and AFT-MXIV-06, respectively.

Study AFT-MXIV-01 was a single-dose, randomized, five-way cross-over study to evaluate the PK of Combogesic IV (acetaminophen 1000 mg and ibuprofen 300 mg), intravenous ibuprofen 300 mg, intravenous acetaminophen 1000 mg, Combogesic IV half dose, and 2 x FDC 500/150 (acetaminophen 500 mg and ibuprofen 150 mg per tablet) tablets in 30 healthy male and female volunteers. This study was to characterize the PK of Combogesic IV, identify whether a PK drug interaction exists between intravenous acetaminophen and intravenous ibuprofen, determine dose proportionality between the full dose and the half dose of Combogesic IV, and to determine the comparative bioavailability of Combogesic IV in comparison to FDC 500/150 tablets.

AFT-MXIV-06 was a single-dose, randomized, four-way cross-over study to evaluate and compare the PK of Combogesic IV to that of Ofirmev (intravenous acetaminophen 1000 mg) and Caldolor (intravenous ibuprofen 400 mg), and to determine the comparative bioavailability of Combogesic IV in comparison to 3 x Combogesic (acetaminophen 325 mg/ibuprofen 97.5 mg per tablet) tablets (aka FDC 325/97.5 tablet) in 30 healthy male and female volunteers.

Acetaminophen and ibuprofen Cmax values were observed at the end of 15-min intravenous infusion for Combogesic IV. Median (min, max) Tmax values of acetaminophen and ibuprofen for FDC 500/150 tablets were 0.75 (0.167, 1.5) h and 1.25 (0.33, 4.0) h, respectively. Median (min, max) acetaminophen and ibuprofen Tmax values for Combogesic tablets were 0.8 (0.3-3.0) h and 1.5 (0.5, 6.0) h, respectively.

Combogesic IV exhibited approximately 2-fold greater Cmax while similar AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to 2 x FDC 500/150 in Study AFT-MXIV-01 (**Table 5**) or 3 x Combogesic tablets in Study AFT-MXIV-06 (**Table 6**).

Table 5 Summary of Acetaminophen Pharmacokinetic Parameters for Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen), Acetaminophen IV (1000 mg), Combogesic IV Half dose, and 2 x FDC 500/150 Tablets and Ibuprofen Pharmacokinetic Parameters for Combogesic IV, Ibuprofen IV (300 mg), Combogesic IV Half dose, and 2 x FDC 500/150 Tablets (500 mg acetaminophen and 150 mg ibuprofen per tablet) (Study AFT-MXIV-01)

	Treatment (Mean ± SD)			
Acetaminophen	**Combogesic® IV (Treatment A)**	**Acetaminophen IV (Treatment B)**	**Combogesic® IV Half dose (Treatment D)**	**FDC 500/150 Tablets (Treatment E)**
C_{max} (ng/mL)	26709.57 ± 5814.74	26236.06 ± 5430.52	12880.39 ± 2553.15	14907.16 ± 6255.10
AUC_{0-t} (ng.h/mL)	37553.97 ± 9816.96	35846.20 ± 8734.15	18327.40 ± 4758.34	34980.80 ± 9430.21
$AUC_{0-\infty}$ (ng.h/mL)	39419.95 ± 10630.63	37651.43 ± 9454.60	19337.01 ± 5146.46	37023.82 ± 10388.31
T_{max} (h)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.02	0.73 ± 0.42
$t_{1/2}$ (h)	2.39 ± 0.27	2.38 ± 0.25	2.44 ± 0.25	2.51 ± 0.33
Ibuprofen	**Combogesic® IV (Treatment A)**	**Ibuprofen IV (Treatment C)**	**Combogesic® IV Half dose (Treatment D)**	**FDC 500/150 Tablets (Treatment E)**
C_{max} (ng/mL)	39506.69 ± 6874.06	40292.97 ± 7460.04	20352.05 ± 3090.87	19637.38 ± 5178.29
AUC_{0-t} (ng.h/mL)	73492.69 ± 16509.61	72169.59 ± 15608.70	39642.48 ± 9679.16	70417.75 ± 16260.16
$AUC_{0-\infty}$ (ng.h/mL)	74743.31 ± 17388.69	73410.65 ± 16500.76	40333.88 ± 10240.30	72202.48 ± 17445.46
T_{max} (h)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.49 ±0.89
$t_{1/2}$ (h)	1.88 ± 0.28	1.87 ± 0.27	1.88 ± 0.30	1.99 ± 0.36

(Source: 2.7.1 Summary of Biopharmaceutic Studies p. 5/18)

Note: Acetaminophen and ibuprofen Tmax values for intravenous administrations were at the end of infusion: 15 min for Combogesic IV, Ibuprofen IV and Combogesic IV half dose. Median (min, max) Tmax values of acetaminophen and ibuprofen for FDC 500/150 were 0.75 (0.167, 1.5) h and 1.25 (0.33, 4.0) h, respectively.

Table 6 Summary of Acetaminophen Pharmacokinetic Parameters for Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen), Ofirmev (1000 mg acetaminophen), and 3 x Combogesic Tablets (aka FDC 325/97.5 Tablets, 325 mg acetaminophen and 97.5 mg ibuprofen per tablet) and Ibuprofen Pharmacokinetic Parameters for Combogesic IV, Caldolor (400 mg ibuprofen), and 3 x Combogesic Tablets (Study AFT-MXIV-06)

	Treatment (Mean ± SD)		
Acetaminophen	**Combogesic® IV (Treatment A)**	**Ofirmev® (Treatment B)**	**FDC 325/97.5 Tablets (Treatment D)**
C_{max} (ng/mL)	25652.6 ± 6643.6	25953.1 ± 5575.4	13469.6 ± 4421.4
AUC_{0-t} (ng.h/mL)	48189.0 ± 12002.7	44423.2 ± 9396.8	39771.1 ± 10415.0
AUC_{0-inf} (ng.h/mL)	50532.1 ± 13083.0	46494.0 ± 10125.7	42278.0 ± 11570.3
T_{max} (h)	0.0 ± 0.0	0.0 ± 0.0	2.6 ± 0.4
$t_{1/2}$ (h)	2.4 ± 0.3	2.4 ± 0.3	2.6 ± 0.4
Ibuprofen	**Combogesic® IV (Treatment A)**	**Caldolor® (Treatment C)**	**FDC 325/97.5 Tablets (Treatment D)**
C_{max} (ng/mL)	43900.7 ± 6158.5	43508.4 ± 6132.8	20401.5 ± 4465.4
AUC_{0-t} (ng.h/mL)	87373.1 ± 16094.2	98804.1 ± 16344.7	73505.6 ± 14639.3
AUC_{0-inf} (ng.h/mL)	88814.5 ± 16606.1	100250.7 ± 16754.7	75510.6 ± 15744.3
T_{max} (h)	0.0 ± 0.0	0.0 ± 0.0	2.0 ± 1.3
$t_{1/2}$ (h)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.4

Note: Acetaminophen and ibuprofen Tmax values for intravenous administrations were at the end of infusion: 15 min for Combogesic IV and Ofirmev, 30 min for Caldolor. Median (min, max) acetaminophen and ibuprofen Tmax values for FDC 325/97.5 tablets were 0.8 (0.3, 3.0) h and 1.5 (0.5, 6.0) h, respectively (source: CSR/MXIV-06 Table 23 and Table 29).

(3). Dose Proportionality between Combogesic IV Full Dose and Combogesic IV Half Dose (Results from Study AFT-MXIV-01)

Following a single dose administration of Combogesic IV full dose (acetaminophen 1000 mg and ibuprofen 300 mg) and Combogesic IV half dose (acetaminophen 500 mg and ibuprofen 150 mg) to healthy volunteers, acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf values were dose proportional. The geometric mean ratios (90% confidence intervals) for Combogesic IV full dose/Combogesic IV half dose for acetaminophen Cmax, AUC0-t, and AUC0-inf were 206.89% (196.27%-218.08%), 204.49% (199.31%-209.79%), and 203.41% (198.37%-208.58%), respectively. The geometric mean ratios (90% confidence interval) for ibuprofen Cmax, AUC0-t, and AUC0-inf were 193.49% (185.70%-201.61%), 185.84% (181.10%-190.71%), and 185.81% (180.90%-190.86%), respectively (**Table 9**).

(4). No PK Drug Interaction between Intravenous Acetaminophen and Intravenous Ibuprofen in Combogesic IV (Results from Study AFT-MXIV-01)

No PK drug interaction between intravenous acetaminophen and intravenous ibuprofen were found in Combogesic IV. Acetaminophen and ibuprofen PK for Combogesic IV (acetaminophen 1000

mg and ibuprofen 300 mg) were bioequivalent to 1000 mg intravenous acetaminophen and 300 mg intravenous ibuprofen given alone, respectively. The point estimates and 90% confidence intervals for acetaminophen and ibuprofen Cmax, AUC0-t and AUC0-inf ratios (Combogesic IV/intravenous acetaminophen and Combogesic IV/intravenous ibuprofen) fell within the 80 to 125% bioequivalence range. The geometric mean ratios (90% confidence intervals) for Combogesic IV/intravenous acetaminophen for acetaminophen Cmax, AUC0-t, and AUC0-inf were 101.67% (95.97%-107.72%), 104.24% (101.42%-107.13%), and 104.15% (101.13%-107.26%), respectively. The geometric mean ratios (90% confidence intervals) for Combogesic IV/intravenous ibuprofen for ibuprofen Cmax, AUC0-t, and AUC0-inf were 98.30% (93.82%-102.99%), 101.57% (98.35%-104.89%), and 101.55% (98.21%-105.00%), respectively (**Table 8**).

(5). Pediatric Plan

The Agency agreed with the sponsor's iPSP with a deferral of all assessments of safety and effectiveness of Combogesic IV for (b) (4) in the communication dated 3/9/2020.

2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication?

For the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. Combogesic IV is indicated for short-term use of five days or less.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Acetaminophen 1000 mg/ibuprofen 300 mg administered as 15-min infusion every 6 hours, as necessary. Do not exceed a total daily dose of 4000 mg of acetaminophen from all sources

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

As of today (5/23/2022), 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:

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1 Combogesic IV Formulation

The Applicant provided the following composition of the dosage form in **Table 7**.

Table 7 Composition of Combogesic IV

Name of ingredient	Function	Formula per unit (100 mL)	Formula per mL	Quality Standard
Acetaminophen (1)	Active ingredient	1000.00 mg	10.00 mg	USP
Ibuprofen sodium dihydrate	Active ingredient	385.00 mg (2)	3.85 mg (3)	USP
Mannitol	(b) (4)	3285.00 mg	32.85 mg	USP
Disodium phosphate dihydrate		13.0 mg	0.13 mg	USP
Cysteine hydrochloride monohydrate		25.00 mg	0.25 mg	USP
Hydrochloric acid (4)	pH adjuster	q.s. pH 6.3-7.3	q.s. pH 6.3-7.3	(4)
Sodium hydroxide (4)	pH adjuster	q.s. pH 6.3-7.3	q.s. pH 6.3-7.3	(4)
Water for Injection	(b) (4)	q.s. 100 mL	q.s. 1 mL	USP
(b) (4)	(b) (4)	q.s.	q.s.	N.F.

(1): United States Adopted Name (USAN) for Paracetamol.
(2): equivalent to 300 mg of ibuprofen.
(3): equivalent to 3 mg of ibuprofen.
(4): Hydrochloric acid (b) (4) and sodium hydroxide (b) (4) are used for pH adjustment and are prepared with Hydrochloric acid N.F. and Sodium hydroxide NF.

(Source: m2\23-qos\drug-product-acetaminophenibuprofen-smf.pdf; p. 1/110)

3.1.2 What is proposed route of administration for Combogesic IV?

The proposed route of administration is stated as IV infusion.

3.2 Clinical Pharmacology Review Questions

3.2.1 Is there a PK drug interaction between intravenous acetaminophen and intravenous ibuprofen in Combogesic IV, is dose proportional between Combogesic IV full dose and Combogesic IV half dose, and what is the comparative bioavailability between Combogesic IV and FDC 500/150 tablets in Study AFT-MXIV-01?

No PK drug interaction between intravenous acetaminophen and intravenous ibuprofen were found in Combogesic IV. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf for Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen) were bioequivalent to 1000 mg intravenous acetaminophen and intravenous 300 mg ibuprofen given alone, respectively. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf were shown to be dose proportional between Combogesic IV full dose and Combogesic IV half dose. Combogesic IV exhibited approximately 2-fold greater Cmax while AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to 2 x FDC 500/150 tablets.

Study AFT-MXIV-01 was a single-dose, randomized, five-way cross-over study to evaluate the pharmacokinetic parameters of Combogesic IV, intravenous ibuprofen, intravenous

acetaminophen, and FDC 500/150 tablets in 30 healthy male and female volunteers. This study was to characterize the PK of Combogesic IV, identify whether a PK drug interaction exists between intravenous acetaminophen and intravenous ibuprofen, determine dose proportionality between the full dose with the half dose of Combogesic IV, and to assess the comparative bioavailability of Combogesic IV in comparison to FDC 500/150 tablets.

Subjects were administered single doses of each of the following treatments in a randomized, cross-over fashion with a washout period of at least 48 hours between treatments:

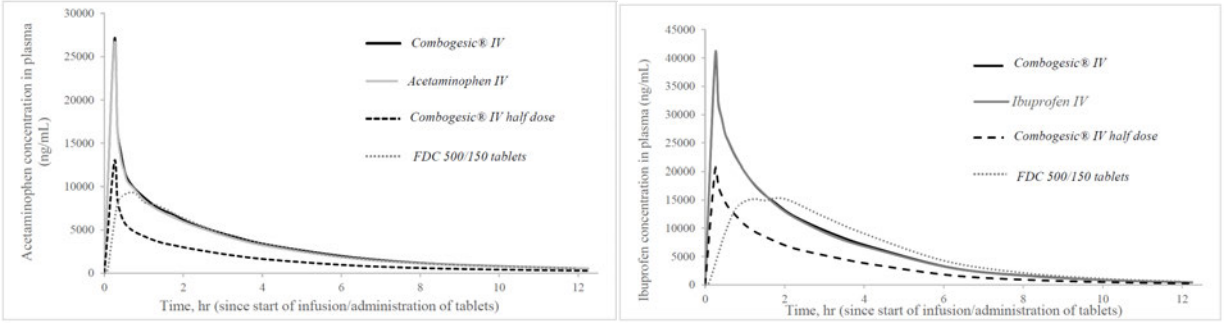
- **Treatment A**: Combogesic IV (acetaminophen 1000 mg + ibuprofen 300 mg in 100mL)
- **Treatment B**: Intravenous acetaminophen 1000 mg in 100 mL infusion
- **Treatment C**: Intravenous ibuprofen 300 mg in 100 mL infusion
- **Treatment D**: Half dose Combogesic IV (acetaminophen 500 mg + ibuprofen 150 mg in 100 mL infusion)
- **Treatment E**: Two FDC 500/150 tablets (each tablet containing acetaminophen 500 mg + ibuprofen 150 mg)

Each intravenous study formulation was administered as a single intravenous dose, infused over 15 minutes. The tablet formulation (Treatment E) was administered orally.

For the intravenous formulation, blood samples were drawn at pre-dose, at the end of the 15-minute infusion, and at 5, 10, 15, 20, 30, 45 minutes, and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the completion of the infusion. For the tablet formulation, blood samples were drawn at pre-dose and at 5, 10, 20, 30, 45 minutes, and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the administration of the study drug.

Mean acetaminophen and ibuprofen plasma concentration-time profiles are presented in **Figure 1**.

Figure 1 Mean acetaminophen plasma concentration-time profiles after single administration of treatment A (Combogesic IV: acetaminophen 1000 mg, ibuprofen 300 mg), treatment B (intravenous acetaminophen 1000 mg), Treatment D (half dose of Combogesic IV: acetaminophen 500 mg, ibuprofen 150 mg), and treatment E (two FDC 500/150 tablets: acetaminophen 1000 mg, ibuprofen 300 mg) (**Left**) and Mean ibuprofen plasma concentration-time profiles after single administration of treatment A (Combogesic IV: acetaminophen 1000 mg, ibuprofen 300 mg), treatment C (intravenous ibuprofen 300 mg), Treatment D (half dose of Combogesic IV: acetaminophen 500 mg, ibuprofen 150 mg), and treatment E (two FDC 500/150 tablets: acetaminophen 1000 mg, ibuprofen 300 mg) (**Right**)



(source: 2.7.1 Summary of Biopharmaceutic Study p. 3/18)

The PK parameters for acetaminophen and ibuprofen are summarized in **Table 5** in **Executive Summary**. Statistical assessment of acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf for Combogesic IV versus individual intravenous components, Combogesic IV versus Combogesic IV half dose, and Combogesic IV versus FDC 500/150 tablets are shown in **Tables 8-10** below.

Following a single dose administration of Combogesic IV, acetaminophen and ibuprofen PK profiles were similar to that observed for the individual intravenous components. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf (**Table 5**) were bioequivalent between Combogesic IV and individual components. The point estimates and the 90% confidence intervals for acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf ratios between Combogesic and individual intravenous components fell within the 80% to 125% bioequivalence range. The geometric mean ratios (90% confidence interval) for Combogesic IV/intravenous acetaminophen for acetaminophen Cmax, AUC0-t, and AUC0-inf were 101.67% (95.97%-107.72%), 104.24% (101.42%-107.13%), and 104.15% (101.13%-107.26%), respectively. The geometric mean ratios (90% confidence interval) for Combogesic IV/intravenous ibuprofen for ibuprofen Cmax, AUC0-t, and AUC0-inf were 98.30% (93.82%-102.99%), 101.57% (98.35%-104.89%), and 101.55% (98.21%-105.00%), respectively (**Table 8**). The results indicated that there was no PK drug interaction when intravenous acetaminophen and intravenous ibuprofen were given in combination. In an in vitro study 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).

Table 8 Statistical Assessment of Acetaminophen PK Parameters between Combogesic IV (Treatment A) and Intravenous Acetaminophen (Treatment B) and Ibuprofen PK Parameters Between Combogesic IV (Treatment A) and Intravenous Ibuprofen (Treatment C)

	Acetaminophen (Treatment A/B)	**Ibuprofen (Treatment A/C)**
C_{max}	101.67 (95.97 – 107.72) [a]	98.30 (93.82 – 102.99) [a]
AUC_{0-t}	104.24 (101.42 – 107.13) [a]	101.57 (98.35 – 104.89) [a]
$AUC_{0-\infty}$	104.15 (101.13 – 107.26) [a]	101.55 (98.21 – 105.00) [a]

[a] Within bioequivalence range

(Source: 2.7.1 Summary of Biopharmaceutic Studies p. 6/18)

Following a single dose administration of Combogesic IV full dose (acetaminophen 1000 mg and ibuprofen 300 mg) and Combogesic IV half dose (acetaminophen 500 mg and ibuprofen 150 mg), acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf values were dose proportional. The geometric mean ratios (90% confidence intervals) for Combogesic IV full dose/Combogesic half dose for acetaminophen Cmax, AUC0-t, and AUC0-inf were 206.89% (196.27%-218.08%), 204.49% (199.31%-209.79%), and 203.41% (198.37%-208.58%), respectively. The geometric

mean ratios (90% confidence intervals) for ibuprofen Cmax, AUC0-t, and AUC0-inf were 193.49% (185.70%-201.61%), 185.84% (181.10%-190.71%), and 185.81% (180.90%-190.86%) (**Table 9**).

Table 9 Dose proportionality of Combogesic IV full dose (Treatment A) vs Combogesic IV half dose (Treatment D)

	Acetaminophen (Treatment A/D)	**Ibuprofen (Treatment A/D)**
C_{max}	206.89 (196.27 – 218.08)	193.49 (185.70 – 201.61)
AUC_{0-t}	204.49 (199.31 – 209.79)	185.84 (181.10 – 190.71)
$AUC_{0-\infty}$	203.41 (198.37 – 208.58)	185.81 (180.90 – 190.86)

(Source: 2.7.1 Summary of Biopharmaceutic Studies p. 6/18)

Acetaminophen and ibuprofen Cmax values were observed at the end of 15-min intravenous infusion for Combogesic IV. Median (min, max) Tmax values of acetaminophen and ibuprofen for FDC 500/150 tablets were 0.75 (0.167, 1.5) h and 1.25 (0.33, 4.0) h, respectively. Combogesic IV exhibited approximately 2-fold greater Cmax while similar AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to 2 x FDC 500/150 (**Table 5**). Acetaminophen and ibuprofen AUC0-inf from Combogesic IV and 2 x FDC 500/150 tablets met the bioequivalence criteria. The geometric mean ratios (90% confidence intervals) for FDC 500/150 vs Combogesic IV for acetaminophen and ibuprofen AUC0-inf were 93.78% (90.98%-96.67%) and 96.45% (93.14%-99.89%), respectively (**Table 10**).

Table 10 Bioavailability of FDC 500/150 (Treatment E) in Comparison to Combogesic IV (Treatment A)

	FDC 500/150 Tablets [a] (Treatment E)	**Combogesic IV [a] (Treatment A)**	**Relative Bioavailability (Treatment E/A)**
Acetaminophen $AUC_{0-\infty}$ (ng.h/ml)	35721.16	38091.23	93.78 (90.98 – 96.67) [b]
Ibuprofen $AUC_{0-\infty}$ (ng.h/ml)	70233.598	72814.966	96.45 (93.14 – 99.89) [b]

[a] Geometric mean
[b] Within bioequivalence range
(Source: 2.7.1 Summary of Biopharmaceutic Studies p. 6/18)

***Reviewer's Comment**: At the Pre-NDA meeting, regarding the use of clinical safety data obtained from FDC 500/150 tablets, the division recommended "Safety data from studies of the oral formulation are not directly supportive of the IV formulation due to the approximately two-fold higher Cmax achieved for ibuprofen and acetaminophen as well as the much more rapid rise in levels for these two active ingredients as compared to the oral formulation administered at a similar dose".*

3.2.2 What is the comparative bioavailability of Combogesic in comparison to Ofirmev, Caldolor, and Combogesic tablets in Study AFT-MXIV-06?

PK comparisons were made between the proposed Combogesic IV and Ofirmev and Caldolor, the listed drug products proposed at an earlier time. Acetaminophen Cmax, AUC0-t and AUC0-inf for Combogesic IV (acetaminophen 1000 mg and ibuprofen 300 mg) and Ofirmev (acetaminophen 1000 mg) were bioequivalent. Ibuprofen Cmax, AUC0-t, and AUC0-inf for Combogesic IV and Caldolor (ibuprofen 400 mg) were comparable. Combogesic IV exhibited approximately 2-fold greater Cmax but similar AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to 3 x Combogesic tablets.

AFT-MXIV-06 was a single-dose, randomized, four-way cross-over study to evaluate and compare the pharmacokinetic parameters of Combogesic IV to that of Ofirmev (intravenous acetaminophen 1000 mg) and Caldolor (intravenous ibuprofen 400 mg), and to determine the comparative bioavailability of Combogesic (acetaminophen 325 mg/ibuprofen 97.5 mg) tablets versus that of Combogesic IV in 30 healthy male and female volunteers. Subjects were administered single dose of each of the following treatments in a randomized crossover fashion with a minimum washout period of 48 hours between treatments:

- **Treatment A**: Combogesic IV (acetaminophen 1000 mg + intravenous ibuprofen 300 mg in 100mL infusion)
- **Treatment B**: Ofirmev (intravenous acetaminophen 1000 mg in 100mL infusion)
- **Treatment C**: Caldolor (intravenous ibuprofen 400 mg in 4 mL infusion)
- **Treatment D**: Three FDC 325/97.5 tablets (each tablet containing acetaminophen 325 mg + ibuprofen 97.5 mg)

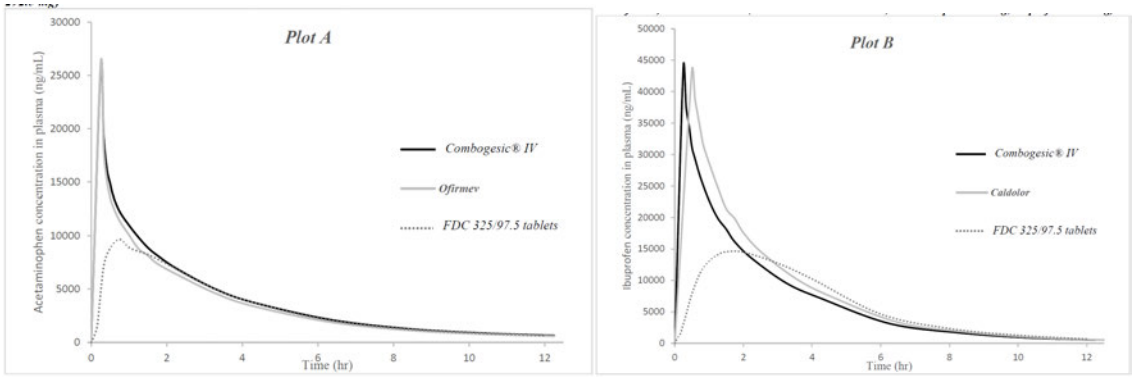
Combogesic IV (Treatment A) and Ofirmev (Treatment B) were administered as an intravenous infusion over 15 minutes. Caldolor (Treatment C) was administered as an intravenous infusion over 30 minutes. The FDC 325/97.5 tablets were administered orally.

For the intravenous products (Treatments A, B, and C), blood samples were collected at pre-dose, one at the end of the intravenous infusion (15 minutes for Treatments A and B, and 30 minutes for Treatment C), and at 5, 10, 15, 20, 30, 45 minutes and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after completion of the infusion. For FDC 325/97.5 tablets (Treatment D), blood samples were collected at pre-dose and at 5, 10, 20, 30, 45 minutes and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-dose.

Mean acetaminophen and ibuprofen plasma concentration versus time profile are shown in **Figure 2**.

Figure 2 Mean acetaminophen plasma concentration-time profiles after single administration of Treatment A (Combogesic IV: acetaminophen 1000 mg, ibuprofen 300 mg in 100 mL infusion), Treatment B (Ofirmev acetaminophen 1000 mg in 100 mL infusion), Treatment D (three FDC 325/97.5: acetaminophen 975 mg, ibuprofen 292.5 mg) (**Plot A on Left**) and Mean ibuprofen plasma concentration-time profiles after single administration of Treatment A (Combogesic IV: acetaminophen 1000 mg, ibuprofen 300 mg in 100 mL infusion), Treatment C (Caldolor ibuprofen

400 mg in 4 mL infusion), Treatment D (three FDC 325/97.5: acetaminophen 975 mg, ibuprofen 292.5 mg) (**Plot B on Right**)



(source: 2.7.1 Summary of Biopharmaceutic Studies p. 9/18)

The PK parameters for acetaminophen and ibuprofen are summarized in **Table 6** in **Executive Summary**. Statistical assessment of acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf for Combogesic IV versus Ofirmev, Combogesic IV versus Caldolor, and Combogesic IV versus Combogesic tablets are shown in **Tables 11-14**.

Acetaminophen and ibuprofen Tmax values were at the end of infusion for intravenous products (i.e., 15 min for Combogesic and Ofirmev, 30 min for Caldolor). Acetaminophen Cmax, AUC0-t, and AUC0-inf values were bioequivalent between Combogesic IV and Ofirmev. The point estimates of the geometric mean ratios (Combogesic IV/Ofirmev) for acetaminophen Cmax, AUC0-t and AUC0-inf were 98.17%, 107.79%, and 107.79%, respectively. The corresponding 90% confidence intervals were 89.21 – 108.03%, 104.63 – 111.05%, and 104.66 – 111.24%, respectively. All these 90% CIs fell within the 80 to 125% bioequivalence range (**Table 11**). Ibuprofen Cmax, AUC0-t, and AUC0-inf values were comparable between Combogesic IV and Caldolor. The point estimates of the geometric mean ratios (Combogesic IV/Caldolor) for ibuprofen Cmax, AUC0-t and AUC0-inf were 101.07%, 88.25%, and 88.34%, respectively. The corresponding 90% confidence intervals were 94.83 – 107.72%, 84.75 – 91.89%, and 84.73 – 92.10%, respectively. All these 90% confidence intervals fell within the 80 to 125% bioequivalence range (**Table 12**).

Table 11: Bioavailability of Acetaminophen for Combogesic in comparison to Ofirmev

Pharmacokinetic Parameter	90% Confidence intervals of geometric means		
	Point Estimate %	Lower Limit %	Upper Limit %
Cmax	98.17	89.21	108.03
AUC $_{0\text{-}t}$	107.79	104.63	111.05
AUC $_{0\text{-}inf}$	107.79	104.66	111.24

(source: 2.7.1 Summary of Biopharmaceutic Studies p.10/18)

Table 12: Bioavailability of Ibuprofen for Combogesic in comparison to Caldolor

Pharmacokinetic Parameter	90% Confidence intervals of geometric means		
	Point Estimate %	Lower Limit %	Upper Limit %
Cmax	101.07	94.83	107.72
AUC $_{0-t}$	88.25	84.75	91.89
AUC $_{0-inf}$	88.34	84.73	92.10

(source: 2.7.1 Summary of Biopharmaceutic Studies p.11/18)

Acetaminophen and ibuprofen Cmax values were observed at the end of 15-min intravenous infusion for Combogesic IV. Median (min, max) acetaminophen and ibuprofen Tmax values for Combogesic tablets were 0.8 (0.3-3.0) h and 1.5 (0.5, 6.0) h, respectively. Combogesic IV exhibited approximately 2-fold greater Cmax while similar AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to 3 x Combogesic tablets (**Table 6**). The point estimates of the geometric mean ratios (Combogesic IV/3 x FDC 325/97.5) for acetaminophen Cmax, AUC0-t and AUC0-inf were 195.03%, 121.65%, and 120.08%, respectively. The corresponding 90% confidence intervals were 177.22 – 214.64%, 118.08 – 125.33%, and 116.47 – 123.80%, respectively. The point estimates of the geometric mean ratios (Combogesic IV/3 x FDC 325/97.5) for ibuprofen Cmax, AUC0-t and AUC0-inf were 218.37%, 119.36%, and 118.29%, respectively. The corresponding 90% confidence intervals were 204.88 – 232.74%, 114.63 – 124.30 %, and 113.46 – 123.33%, respectively (**Tables 13** and **14**).

Table 13: Comparative Bioavailability of Acetaminophen for Combogesic IV vs FDC 325/97.5

Pharmacokinetic Parameter	90% Confidence intervals of geometric means		
	Point Estimate %	Lower Limit %	Upper Limit %
Cmax	195.03	177.22	214.64
AUC $_{0-t}$	121.65	118.08	125.33
AUC $_{0-inf}$	120.08	116.47	123.80

(source: 2.7.1 Summary of Biopharmaceutic Studies p.11/18)

Table 14: Comparative Bioavailability of Ibuprofen for Combogesic IV vs FDC 325/97.5

Pharmacokinetic Parameter	90% Confidence intervals of geometric means		
	Point Estimate %	Lower Limit %	Upper Limit %
Cmax	218.37	204.88	232.74
AUC $_{0\text{-}t}$	119.36	114.63	124.30
AUC $_{0\text{-}inf}$	118.29	113.46	123.33

(source: 2.7.1 Summary of Biopharmaceutic Studies p.11/18)

***Reviewer's Comments**: The sponsor assessed comparative bioavailability of Combogesic IV in comparison with the original identified listed drug product including IV single entity products Ofirmev (acetaminophen 10 mg/mL, NDA 22450) and Caldolor (ibuprofen 800 mg/8 mL, NDA 22348). The sponsor stated in their Pre-NDA meeting package that for commercial reasons they decided that it cannot refer to these listed drugs and proposed Ultracet (NDA 21123) and Motrin (NDA 17463) as listed drug products. Therefore, although the PK comparison from Combogesic IV to Ofirmev and Caldolor is described in the review, it should not be used to support approval of this product.*
The sponsor was recommended "Although it would be acceptable to reference the oral products Ultracet and Motrin in support of your NDA for Combogesic IV, additional safety data will be required if the exposures achieved with Combogesic IV exceed those of the individual components with the referenced products (i.e., with regard to Cmax) administered according to approved labeling". In addition, regarding the use of clinical safety data obtained from Combogesic tablet, the division recommended "Safety data from studies of the oral formulation are not directly supportive of the IV formulation due to the approximately two-fold higher Cmax achieved for ibuprofen and acetaminophen as well as the much more rapid rise in levels for these two active ingredients as compared to the oral formulation administered at a similar dose".

3.2.3 What is comparative bioavailability of Combogesic IV in comparison to Ultracet and IBU in Study AFT-MXIV-12?

In support of the 505(b)(2) application, pharmacokinetic comparisons were made between the proposed Combogesic IV and listed drug Ultracet (acetaminophen 325 mg + tramadol HCl 37.5 mg per tablet, 2 tablets for a full dose) (NDA 21123) and IBU tablet (ibuprofen 800 mg per tablet, 1 tablet for a full dose) (ANDA 75682), a generic product to the listed drug Motrin.

Median (min, max) Tmax values of acetaminophen and ibuprofen for Combogesic IV were at the end of 15-min intravenous infusion (i.e., 0.25 (0.17-0.33) h) and they were shorter than median (min, max) Tmax values of acetaminophen for Ultracet (i.e., 0.5 (0.33-2.0) h) and median (min, max) Tmax values of ibuprofen for IBU (i.e., 1.50 (0.75-4.0) h). The mean acetaminophen half-life values for Combogesic IV and Ultracet were similar (e.g., 2.5 h for Combogesic IV and 2.7 h for Ultracet). Mean ibuprofen half-life values for Combogesic IV and IBU were similar (e.g., 2.2 h for Combogesic IV and 2.1 h for IBU) (**Tables 1** and **2** in **Executive Summary**).

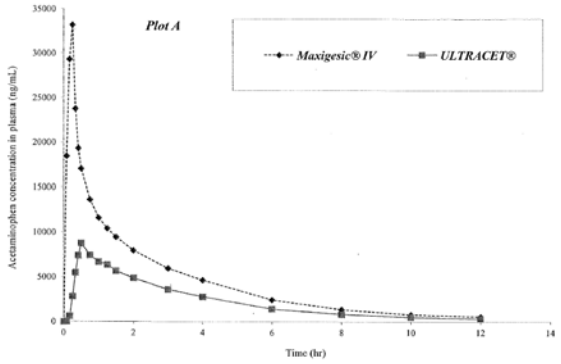
Combogesic IV exhibits 3.1-fold greater acetaminophen Cmax and 2-fold greater acetaminophen AUC0-t and AUC0-inf values in comparison to 2 x Ultracet tablets; Combogesic IV exhibits similar ibuprofen Cmax and 55% lower AUC0-t and AUC0-inf values than those from 1 x IBU tablet (**Tables 3** and **4** in **Executive Summary**). The dose normalized Cmax, AUC0-t, and AUC0-inf values of acetaminophen (Cmax/dose, AUC0-t/dose and AUC0-inf/dose) for Combogesic IV were 2-fold, 30%, and 28% greater than those for Ultracet. The dose normalized Cmax and AUC0-t of ibuprofen for Combogesic IV were 2.4-fold and 21% greater than those for IBU, while dose normalized AUC0-inf of ibuprofen was comparable to IBU because the 90% confidence intervals fell within the 80 to 125% bioequivalence range. (**Tables 3** and **4**). Greater dose normalized exposures to acetaminophen and ibuprofen with Combogesic IV were mainly attributed to differences in the routes of administration.

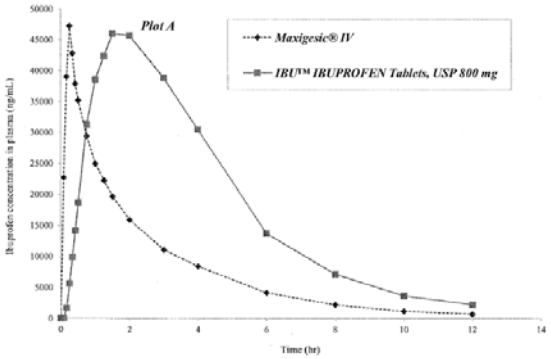
Study AFT-MXIV-12 was a single-dose, randomized, three-way cross-over study to evaluate and compare the pharmacokinetic parameters of Combogesic IV, 2 x Ultracet tablets (acetaminophen 325 mg/tablet + tramadol hydrochloride 37.5 mg/tablet), and 1 x IBU (ibuprofen 800 mg/tablet) in 30 healthy male volunteers. The listed drug product Motrin was discontinued not for safety or efficacy reasons. A generic of Motrin, IBU tablet, was used as the comparator in this study. Subjects were administered single doses of each of the following treatments in a randomized cross-over fashion with a minimum washout period of 3 days between treatments:

- **Treatment A**: Combogesic IV (acetaminophen 1000 mg + intravenous ibuprofen 300 mg in 100 mL infusion), infused over 15 minutes
- **Treatment B**: 2 x Ultracet tablets (acetaminophen 325 mg + tramadol hydrochloride 37.5 mg per tablet) administered orally
- **Treatment C**: 1 x IBU tablet (ibuprofen 800 mg per tablet) administered orally

For Combogesic IV treatment, blood samples were collected at pre-dose, 5, 10, and 15 min (i.e., at the end of the intravenous infusion), and at 20, 25, 30, 45 min and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the infusion. For Ultracet and IBU, blood samples were collected at pre-dose and at 5, 10, 15, 20, 25, 30, 45 min and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 h post-dose.
Mean acetaminophen and ibuprofen plasma concentration-time profiles are shown in **Figure 3**.

Figure 3: Mean Acetaminophen Plasma Concentration-Time Profiles after single dose administration of Combogesic IV (acetaminophen 1000 mg, ibuprofen 300 mg, administered by intravenous infusion for 15 minutes) and 2 x Ultracet (acetaminophen 650 mg and tramadol hydrochloride 75 mg administered orally) (**Left**) and Mean Ibuprofen Plasma Concentration-Time Profiles after single dose administration of Combogesic IV (acetaminophen 1000 mg, ibuprofen 300 mg, administered by intravenous infusion for 15 minutes) and 1 x IBU (ibuprofen 800 mg, administered orally) (**Right**)





(Source: 2.7.2 Summary of Biopharmaceutic Studies p.14/18)

The PK parameters for acetaminophen and ibuprofen from Combogesic IV, Ultracet, and IBU are summarized in **Tables 1** and **2** in **Executive Summary**. Statistical assessment of acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf and the dose normalized Cmax, AUC0-t, and AUC0-inf for Combogesic IV versus Ultracet and Combogesic IV versus IBU are shown in **Tables 3** and **4** in **Executive Summary**.

Median (min, max) Tmax values of acetaminophen and ibuprofen for Combogesic IV were at the end of 15-min intravenous infusion (i.e., 0.25 (0.17-0.33) h) and they were shorter than median (min, max) Tmax values of acetaminophen for Ultracet (i.e., 0.5 (0.33-2.0) h) and median (min, max) Tmax values of ibuprofen for IBU (i.e., 1.50 (0.75-4.0) h). The mean acetaminophen half-life values for Combogesic IV and Ultracet were similar (e.g., 2.5 h for Combogesic IV and 2.7 h for Ultracet). Mean ibuprofen half-life values for Combogesic IV and IBU were similar (e.g., 2.2 h for Combogesic IV and 2.1 h for IBU) (**Tables 1** and **2**).

Combogesic IV exhibited 3.1-fold greater acetaminophen Cmax and 2-fold greater acetaminophen AUC0-t and AUC0-inf values than 2 x Ultracet tablets; Combogesic IV exhibited similar ibuprofen Cmax and 55% lower AUC0-t and AUC0-inf values than 1 x IBU tablet (**Tables 3** and **4**).

The dose normalized Cmax, AUC0-t, and AUC0-inf values of acetaminophen (Cmax/dose, AUC0-t/dose and AUC0-inf/dose) for Combogesic IV were 2-fold, 30%, and 28% greater than those for Ultracet. The dose normalized Cmax and AUC0-t of ibuprofen for Combogesic IV were 2.4-fold and 21% greater than those for IBU, while dose normalized AUC0-inf of ibuprofen was similar to that for IBU because the 90% confidence intervals fell within the 80 to 125% bioequivalence range. (**Tables 3** and **4**).

Reviewer's Comments*: The sponsor stated in their Pre-NDA meeting package that for commercial reasons they proposed Ultracet (NDA 21123) and Motrin (NDA 17463) instead of Ofirmev and Caldolor as listed drug products. In Form 356h, the sponsor listed Ultracet (NDA 21123), Motrin (17463), and IBU (ANDA 75682) as listed drugs. Note ANDA product IBU cannot be used as listed drug, it was used as comparator in the PK study because the NDA product, Motrin, was discontinued. The sponsor was recommended "Although it would be acceptable to reference the oral products Ultracet and Motrin in support of your NDA for Combogesic IV, additional safety data will be required if the exposures achieved with Combogesic IV exceed those of the individual*

components with the referenced products (i.e., with regard to Cmax) administered according to approved labeling".

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Acetaminophen and ibuprofen plasma concentrations in Studies AFT-MXIV-01, AFT-MXIV-06, and AFT-MXIV-12 were measured by LC-MS/MS methodology. In Study AFT-MXIV-01, the utilized method had validated calibration curve standards from 50 to 20000 ng/mL and 50 to 35000 ng/mL for acetaminophen and ibuprofen, respectively. The validation of the method included within study validation, linearity testing, limit of quantitation, and quality control samples (150, 2500, 10000, and 15000 ng/mL for acetaminophen and 150, 1250, 12500, 17500, and 27000 ng/mL for ibuprofen). The lower limit of quantitation (LLOQ) in plasma was set at 50 ng/mL for both of acetaminophen and ibuprofen, respectively. In Study AFT-MXIV-06, the utilized method had validated calibration curve standards from 50 to 20000 ng/mL and 200 to 60000 ng/mL for acetaminophen and ibuprofen, respectively. The validation of the method included within study validation, linearity testing, limit of quantitation, and quality control samples (150, 2500, 10000, and 15000 ng/mL for acetaminophen and 600, 7500, 15000, 30000, and 45000 ng/mL for ibuprofen). The LLOQ in plasma was set at 50 ng/mL for acetaminophen and 200 ng/mL for ibuprofen, respectively. In Study AFT-MXIV-12, the utilized method had validated calibration curve standards from 50 to 30000 ng/mL and 300 to 60000 ng/mL for acetaminophen and ibuprofen, respectively. The validation of the method included within study validation, linearity testing, limit of quantitation, and quality control samples (150, 2500, 6000, 15000, and 22500 ng/mL for acetaminophen and 900, 7500, 15000, 30000, and 45000 ng/mL for ibuprofen). The LLOQ in plasma was set at 50 ng/mL for acetaminophen and 300 ng/mL for ibuprofen, respectively. The observed accuracy and precision (%CV) were within <15%.

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