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APPLICATION NUMBER:

203414Orig1s000

PHARMACOLOGY REVIEW(S)

**SUPERVISOR'S MEMO**

Date:	4 Jan 2013
RE:	NDA 203414
Sponsor:	Takeda Pharmaceuticals
Drug/Indication	Alogliptin + Metformin FDC
Reference NDAs	Alogliptin monotherapy (22271) Alogliptin + Pioglitazone FDC (22426)

In 2009, the FDA issued a Complete Response to Takeda for NDA 22271 which sought marketing of alogliptin, a DPP4 inhibitor, as monotherapy for type 2 diabetes. The same regulatory action was taken for the related NDA 22426, a fixed dose combination of alogliptin + pioglitazone. A third NDA, 203414, was subsequently submitted for a fixed dose combination of alogliptin + metformin.

Clinical and nonclinical issues were cited as issues in the CR letter from 2009. The nonclinical issue concerned a potential teratogenicity signal that emerged at that time in studies with another DPP4 inhibitor when used in conjunction with metformin. Because alogliptin would be frequently used in combination with metformin, Takeda was required to submit an embryofetal development study in rats administered alogliptin with and without metformin. This combination study would also support the alogliptin + metformin FDC product.

The requested embryofetal study was submitted by Takeda in their complete response submission for both NDAs (monotherapy and pioglitazone FDC) and in support of the metformin FDC product. No drug-related fetal abnormalities considered relevant to human subjects was identified in a combination embryofetal toxicology study conducted in rats. The study included separate arms for alogliptin and metformin in addition to the drugs in combination, as requested by FDA. Two dams from the high dose combination group of 100/500 mg/kg alogliptin/metformin produced 4 fetuses with abnormalities, but this was associated with evidence of toxicity in the dams. Exposure margins at these doses are approximately 23x for alogliptin and 6x metformin relative to the recommended clinical doses. Of note, the teratogenicity issue (craniofacial abnormalities) that emerged in 2009 with another DPP4 inhibitor was subsequently resolved with additional studies, and no further evidence of augmented teratogenicity has been observed with the combination of DPP4 inhibitors and metformin. The nonclinical CR issue has therefore been adequately addressed by the sponsor and the data supports an approval recommendation for each NDA.

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/s/

TODD M BOURCIER

01/04/2013

p/t recommends AP

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203-414

Supporting document/s: SDN-1(N-000)

Applicant's letter date
(CDER Stamp Date): 22 November, 2011

Product: Alogliptin + metformin FDC (Kazano™)

Indication: type 2 diabetes mellitus (T2DM)

Applicant: Takeda Pharmaceutical Co. Ltd.

Review Division: Metabolism and Endocrinology Products

Reviewer: David B. Carlson, Ph.D.

Supervisor/Team Leader: Todd Bourcier, Ph.D.

Division Director / Mary Parks, M.D.

Deputy Director: Eric Colman, M.D.

Project Manager: Mehreen Hai, Ph.D.

Review Completion Date: 20 July, 2012

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203-414 are owned by Takeda or are data for which Takeda has obtained a written right of reference. Any information or data necessary for approval of NDA 203-414 that Takeda does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203-414.

Review Notes and Abbreviations/Key

Some of the sponsor's tables from the electronic NDA submission have been included and cited in this review. All drug-related trends are discussed in relation to concurrent vehicle control groups in each study unless otherwise noted. Vehicle for oral gavage administration was 0.5% methylcellulose for alogliptin and water for injection (sterile water) for metformin unless otherwise noted. Common animal strains were used and abbreviated by common animal name, unless noted, as follows: Sprague-Dawley rat, CD-1 mouse, Beagle dog, Cynomolgus monkey, New Zealand White rabbit. Alogliptin benzoate salt (SYR-322) and metformin HCl drug substances were used for dosing solutions, with all nominal doses expressed as free base SYR-322Z (SYR-322/SYR-322Z = 1.360) or metformin (metformin HCL/metformin = 1.282). Reviews of some studies previously reviewed under NDA 22-271 and INDs 70,963 and 101,628 are cited and summarized in this NDA review.

Key: Alogliptin benzoate (alo; alogliptin; SYR-322; SYR-322Z; SYR322S), SYR-322Z (free base of SYR-322); metformin HCl (met; metformin); pioglitazone HCl (pio; pioglitazone); glucagon-like peptide 1 (GLP-1); glucose-dependent insulintropic peptide (GIP); fixed-dose combination (FDC), once daily dosing (QD), twice-daily dosing (BID), dosing groups – LD (low dose), MD (mid dose), LMD (low mid dose), HMD (high mid dose), HD (high dose); mg/kg (mg/kg/day); MRHD (maximum recommended human dose); NOAEL (no observed adverse effect level); LOAEL (lowest observed adverse effect level); MTD (maximum tolerated dose); statistically significant (ss); not statistically significant (nss); IR (immediate release), XR (extended release); PD (pharmacodynamic), PK (pharmacokinetic), TK (toxicokinetic); BW (body weight); GD (gestation day); CNS (central nervous system); GI (gastrointestinal tract); CV (cardiovascular); T2DM (type 2 diabetes mellitus).

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1 Executive Summary

1.1 Introduction

The proposed alogliptin plus metformin fixed-dose combination, film-coated tablet was submitted in accordance with 21 USC 505(b)(2) for treatment of type 2 diabetes mellitus as an adjunct to diet and exercise. Alogliptin monotherapy and alogliptin plus pioglitazone FDC NDAs have been previously submitted, reviewed, and received approval recommendations by this pharmacology/toxicology reviewer. Metformin is approved to treat type 2 diabetes as first line monotherapy and in combination with various drugs as FDC formulations. The Sponsor documented a written 'right of reference' to the metformin manufactured (b) (4) (DMF (b) (4)) and provided references to the listed metformin product (Glucophage®).

Alogliptin plus metformin combination toxicity studies were previously submitted and reviewed under the alogliptin monotherapy NDA 22-271. Nonclinical studies assessed coadministration of the proposed drug substances but the exact FDC drug product was not assessed in animals. This pharmacology/toxicology review summarizes pertinent data (including previously reviewed studies) and discusses any nonclinical issues unique to the proposed FDC formulation.

1.2 Brief Discussion of Nonclinical Findings

Prior pharmacology/toxicology reviews for alogliptin monotherapy, with consideration of alogliptin on a background of metformin treatment, based maximum recommended human dose (MRHD) exposure estimates on 25 mg alogliptin with $AUC_{0-24\text{ h}} = 1.5\text{ }\mu\text{g}\cdot\text{h}/\text{ml}$ and 2000 mg metformin with $AUC_{0-24\text{ h}} = 26\text{ }\mu\text{g}\cdot\text{h}/\text{ml}$. The current proposed alogliptin plus metformin FDC tablets are recommended for twice daily dosing with food at 12.5 mg alogliptin/1000 mg metformin, for an equivalent total daily MRHD of 25 mg alogliptin/2000 mg metformin. The Sponsor identified slightly different $AUC_{0-24\text{ h}}$ exposures for their clinical exposure comparisons, using $1.76\text{ }\mu\text{g}\cdot\text{h}/\text{ml}$ alogliptin based on the maximum mean exposure achieved in elderly subjects (i.e., a conservative approach based on maximum alogliptin exposure in a subpopulation). There were no "clinically meaningful" differences in alogliptin exposure by sex, but for the purposes of clinical exposure margin estimates in pregnant women the Sponsor used $AUC_{0-24\text{ h}} = 1.73\text{ }\mu\text{g}\cdot\text{h}/\text{ml}$ for women (mean all ages combined) compared to male $AUC_{0-24\text{ h}} = 1.40\text{ }\mu\text{g}\cdot\text{h}/\text{ml}$ (mean all ages combined).

No adjustments were made for estimated total daily exposures for QD versus BID dosing. A dedicated bioequivalence clinical trial showed there were no clinically meaningful differences in exposure based on single (QD) or twice (BID) daily dosing. Nonclinical studies did not directly investigate differences in QD versus BID dosing but no nonclinical efficacy or safety endpoints were identified to suggest differences from single or twice daily dosing. While total clinical alogliptin exposures (AUC) will be similar

for BID dosing compared to QD, the daily maximum clinical plasma exposure (C_{max}) will be lower. Alogliptin plasma levels after 12.5 mg BID dosing have been shown to be sufficient for clinical DPP4 inhibition and no effect on efficacy is expected with the FDC tablet BID dosing.

The proposed FDC formulation combines a DPP4 inhibitor and a biguanide. The complementary mechanisms for alogliptin- and metformin-induced glucose lowering have been shown to result in clinical therapeutic benefits compared to either drug alone. In addition to the expected improvements in insulin secretion, insulin sensitivity, and appetite by GLP-1 and peripheral insulin sensitivity by metformin, metformin slowed intestinal sugar absorption in diabetic Wistar Fatty rats. Clinical data also show metformin treatment increases plasma GLP-1 independent of DPP4 inhibitor coadministration, likely by stimulating GLP-1 secretion rather than GLP-1 breakdown.

In rats alogliptin plasma exposure (C_{max} and AUC_{0-24h}) consistently decreased slightly, approximately 25-40%, with metformin coadministration. Metformin co-treatment did not affect alogliptin metabolism. Conversely, alogliptin treatment did not alter metformin plasma exposures.

As noted in a prior alogliptin pharmacology/toxicology review, coadministration of metformin at MTD doses with well tolerated alogliptin doses did not show any unexpected toxicity or synergism in rats. Toxicity was generally driven by metformin and included reduced BW gain, plasma lactic acid accumulation without concomitant increased bicarbonate, increased serum ALT and CK, slight alterations in plasma electrolytes, and increased organ weights with correlative histological lesions. Heart cardiomyopathy and myocardial hypertrophy, liver hepatocyte hypertrophy, kidney tubule regeneration and hypertrophy, salivary gland hypertrophy, and adrenal vacuolation and hypertrophy were correlated with organ/tissue weight increases. GI tract was also a target based on stomach gross foci and erosion, duodenum erosion, and cecum hyperplasia.

Pancreatitis has been identified as a potential clinical risk with DPP4 inhibitor use. Comprehensive analyses of nonclinical study reports did not identify any signals of pancreatic toxicity in rodents, dogs, or monkeys treated with alogliptin. Coadministration of metformin with alogliptin also did not have any apparent effect on pancreatic toxicity.

A potential clinical signal for alogliptin-induced liver toxicity has been identified from clinical adverse event reports. Alogliptin animal data have not indicated a strong signal for liver toxicity. Signs of modest liver toxicity were seen in chronic/lifetime rat studies with alogliptin, which showed liver hepatocellular hypertrophy, periportal vacuolation, and basophilic 'focus of cell alteration' at greater than 200-times estimated clinical dose. The NOAEL for hepatotoxicity was at least 30-times MRHD in all animal species (mouse, rat, dog, monkey). Data from combination alogliptin plus metformin toxicity studies did not indicate any signs of increased liver toxicity.

Metformin is excreted unchanged in urine and renal impairment leads to increased metformin exposure through decreased urinary excretion. Increased metformin exposure increases the risk of lactic acidosis, a rare potential clinical adverse event. Renal toxicity was seen only after chronic/lifetime exposure at very high exposure margins in rats (>200X MRHD). There was no nonclinical evidence of increased renal toxicity with alogliptin and metformin coadministration.

DMEP required a combination alogliptin plus metformin rat embryofetal development study to support the alogliptin monotherapy NDA because of potential class-related craniofacial malformations in rats treated with DPP4 inhibitors and metformin. The data showed no treatment related fetal findings in alogliptin or metformin controls or in the low dose combination treatment (34X alogliptin / 3X metformin MRHD at the NOAEL). In the high dose combination treatment group there was evidence of maternal toxicity based on reduced body weight gain. Eye and vertebral malformations were seen in 4 fetuses from 2 (of 20) dams in the 100/500 mg/kg (alogliptin/metformin) combination (23X alogliptin / 6X metformin MRHD). A relationship to treatment could not be ruled out for malformed fetuses, but findings were limited to microphthalmia in three fetuses from one dam with markedly reduced body weight gain (suggesting significant maternal toxicity) and a single fetus with multiple abnormalities in a separate dam (microphthalmia, cleft palate, microglossia, and mandibular micrognathia). There were no other treatment-related malformations and no apparent treatment-related external, visceral, or skeletal variations. There were no apparent treatment-related effects on pregnancy success or other pregnancy-related or fetal outcomes in any group. The fetal malformations were not consistent with prior craniofacial malformation signals in the class. It is important to note that no further evidence of craniofacial abnormalities has emerged in embryofetal studies with DPP4 inhibitor and metformin coadministration.

It is worth noting that metformin treatment alone has been shown to cause embryofetal malformations at 10- to 20-times clinical exposures in Han Wistar rats. Similar results have not been seen in the Sprague Dawley strain used in the alogliptin plus metformin studies. While the Han Wistar strain may be more sensitive to skeletal malformations that were observed, dams in that study also showed signs of metabolic acidosis and mild reductions in plasma glucose coupled with reduced body weight gain. A combination of those effects may have been sufficient to cause fetal malformations in Han Wistar rats. Blood glucose and metabolic acidosis parameters were not assessed in the current study with Sprague Dawley rats, but given sufficiently high metformin exposure similar maternal and fetal effects could be seen in the Sprague Dawley strain. In summary, there was no clear evidence of unexpected or synergistic increases in maternal or embryofetal toxicity and fetal malformations from two high dose alogliptin plus metformin dams were likely incidental or secondary to maternal toxicity.

The pediatric development plan is similar to that proposed for other alogliptin applications. Juvenile animal studies have not been required for other DPP4 inhibitors but Takeda investigated juvenile growth and development in rats treated with alogliptin. Testes-related toxicity was seen in adult monkeys and rats at high exposure multiples (NOAELs>30- to 200-times MRHD) and the juvenile studies included detailed

observations of juvenile male reproductive system development. The alogliptin toxicology profile seems similar in juveniles and adults with a large therapeutic index. There were no apparent alogliptin effects up to 77- or 88-times (male reproductive study) expected clinical exposures. Other potential targets in juveniles are immune system and brain development, but they are developed beyond critical stages in the target 10 to 17 year old age group. Nonclinical data support the safety of alogliptin (with or without metformin) in the proposed pediatric population and no additional nonclinical studies are needed.

Alogliptin is well tolerated in animals with large exposure margins to toxic animal doses and metformin clinical benefits and risks are well established. There is no unique toxicity concern for alogliptin in fixed-dose combination with metformin.

Safety issues relevant to clinical use of alogliptin alone or in combination with metformin were summarized in prior pharmacology/toxicology reviews. Potential toxicity issues that may arise after marketing are reiterated and updated here where appropriate.

1. Hypersensitivity and/or pseudoallergy are predicted in sensitive individuals in the clinical population based on findings in dogs administered alogliptin. The reactions in dogs include facial swelling/edema at high multiples of human exposure ($\geq 32X$ MRHD). The reaction in dogs seemed to be separate from DPP4-inhibitor induction of necrotic skin lesions in monkeys. The risk of skin lesions from prolonged alogliptin treatment cannot be ruled out, but there was no evidence of skin lesions in any species in the non-clinical program.
2. Since DPP4 cleaves substrates other than the targeted incretin hormones, inhibition of DPP4 may have unintended consequences with prolonged dosing. In particular, antigen-mediated responses and immune cell trafficking may be affected by DPP4 inhibition. Immune-related effects remain an unresolved, unavoidable risk with DPP4 inhibitor drugs.
3. Hypoglycemia risk is expected to be low due to the GLP-1 glucose-dependent and metformin insulin-sensitization mechanisms. No hypoglycemia was seen in combination toxicology studies. Nevertheless, clinical hypoglycemia risks may be higher compared to either monotherapy because of the independent, complementary glucose lowering mechanisms of the two drugs.
4. Both alogliptin and metformin are secreted in milk of nursing rats. No nonclinical studies with combination alogliptin and metformin have been conducted during lactation and nursing. Potential effects on growth and development of nursing animals is unknown. Metformin is secreted in human milk in low levels but it is not known if alogliptin is secreted in human milk. The proposed Kazano™ label warns that caution should be exercised when the drug is administered to nursing women.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/toxicology recommends approval. The previous pharmacology/toxicology approval recommendation for alogliptin monotherapy considered nonclinical alogliptin plus metformin toxicity studies and expected alogliptin clinical use on a background of metformin, the first line therapy for type 2 diabetes.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Nonclinical labeling recommendations have been completed for the alogliptin monotherapy label (NDA 22-271). The nonclinical sections in the Kazano™ label will reflect the final monotherapy label for alogliptin and the reference Glucophage® label for metformin. Only specific pregnancy section labeling recommendations for the pregnancy category and the alogliptin plus metformin section are included in this review.

Proposed alogliptin/metformin pregnancy section

8.1 Pregnancy

Pregnancy Category B:

Alogliptin/Metformin hydrochloride

There are no adequate and well-controlled studies in pregnant women with (b) (4) KAZANO or its individual components. Because animal reproduction studies are not always predictive of human response, (b) (4) should (b) (4) be used during pregnancy only if clearly needed.

No treatment-related fetal abnormalities occurred following concomitant administration of 100 mg/kg/day alogliptin with 150 mg/kg/day metformin to pregnant rats (b) (4)



2 Drug Information

2.1 Drug

Kazano™ (proposed) FDC tablets

2.1.1 CAS Registry Number

Alogliptin – 850649-62-6

Metformin HCl – 115-70-4; metformin (free base) 657-24-9

2.1.2 Generic Name

Alogliptin (alogliptin benzoate) and metformin hydrochloride

2.1.3 Code Name

Alogliptin – SYR-322 (SYR-322S; SYR110322; SYR110322S; SYR110322 benzoate)

2.1.4 Chemical Name

Alogliptin – 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)benzonitrile monobenzoate; 2-[[6-[(3*R*)-3-Amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl]methyl]benzonitrile monobenzoate

Metformin HCl – 1,1-dimethylbiguanide hydrochloride;
N,N-Dimethylimidodicarbonimidic diamide hydrochloride

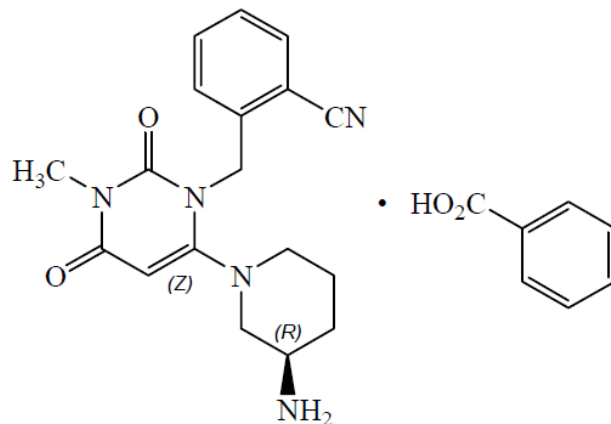
2.1.5 Molecular Formula/Molecular Weight

Alogliptin – C₁₈H₂₁N₅O₂·C₇H₆O₂ / 461.51 g/mol (benzoate salt); 339.30 g/mol (free base)

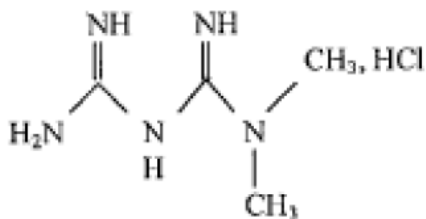
Metformin HCl – C₄H₁₂ClN₅ / 165.62 g/mol

2.1.6 Structure

Alogliptin



Metformin HCl –



2.1.7 Pharmacologic class

Dipeptidyl peptidase IV (DPP4) inhibitor (alogliptin) plus biguanide (metformin).

2.2 Relevant IND/s, NDA/s, and DMF/s

Alogliptin – NDA 22-271 and IND 69,707 (alogliptin); IND 101,628 (alogliptin + metformin); NDA 22-426 and IND 73,193 (alogliptin + pioglitazone)

Metformin – NDA 20-357 (metformin; Glucophage®), NDA 21-748 (metformin; Glumetza®); DMF (b) (4) (metformin XR (b) (4))

DPP4 Inhibitor NDAs – NDA 21-995 (sitagliptin, Januvia®) and NDA 22-044 (sitagliptin + metformin, Janumet®); NDA (b) (4) (vildagliptin); NDA 22-350 (saxagliptin, Onglyza®) and NDA 200-678 (saxagliptin + metformin, Kombiglyze XR ®); NDA 201-280 (linagliptin), NDA 201-281 (linagliptin + metformin)

2.2 Drug Formulation

No new information on alogliptin or metformin drug substances was submitted. The Sponsor cross-referenced their alogliptin monotherapy application, NDA 22-271, and they have a written right of reference to metformin and drug information in DMF (b) (4)

Drug product inactive ingredients are shown in

the Sponsor's summary below (Table 1). All excipients in the drug product are compendial and all of the inactive ingredients, including food-grade pigments, have been previously reviewed for alogliptin formulations or included at higher concentrations in listed oral drugs.

Table 1 – Drug product composition summary

Table 1.b Composition of SYR-322MET Tablets 12.5mg+500mg, and 12.5+1000mg (b) (4)				
Component	Reference to Quality Standards	Function	Quantity per Tablet (mg)	
			(b) (4) 12.5mg +500mg	12.5mg +1000mg (b) (4)
Alogliptin benzoate (As the free base)	In-house standard	Active ingredient	(b) (4) 17 (12.5)	17 (12.5) (b) (4)
Mannitol	Ph.Eur., USP			
Microcrystalline cellulose	Ph.Eur., NF			
Povidone	Ph.Eur., USP (b) (4)			
Metformin hydrochloride	Manufacturer's standard (b)	Active ingredient	(b) (4) 500	1000 (b) (4)
Crospovidone	Ph.Eur., NF (b) (4)			(b) (4)
Magnesium stearate	Ph.Eur., NF (b) (4)			
(a)	(b) (4)			
(b) Also meets USP.				

Table 1.b Composition of SYR-322MET Tablets (b) (4)
12.5mg+500mg, 12.5+1000mg (continued)

Component	Reference to Quality Standards	Function	Quantity per Tablet (mg)		
			(b) (4)	12.5mg +500mg 12.5mg +1000mg	
Film-Coating			(b) (4)		
Hypromellose 2910	Ph.Eur., USP	(b) (4)	(b) (4)		
Talc	Ph.Eur., USP				
Titanium dioxide	Ph.Eur., USP				
(b) (4)					
Ferric oxide, yellow	95/45/EC (E172)., NF				
(b) (4)					
Tablet weight			(b) (4)	730 1350	

(a) (b) (4)
 (b) Also meets USP.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

The CMC reviewer for this application noted an anomaly in the original quality assessment for the alogliptin drug product. The specification for 'degradation products' is (b) (4) for alogliptin tablets ((b) (4) 12.5 mg (b) (4)). The ICH Guidance for Impurities in New Drug Products (Q3B(R2)) lists identification thresholds of 0.5% and 0.2% degradation products for drug products with 1mg to 10 mg or 10 mg to 2 g maximum daily dose, respectively. (b) (4)

(b) (4) No degradation products were detected (b) (4) in 12.5 mg (b) (4) tablets. The reason for the (b) (4) detected was not determined.

Nevertheless, the 0.2% identification threshold was not exceeded for any of the alogliptin tablets.

(b) (4)

(b) (4) Importantly, there are very high safety margins to the proposed alogliptin MRHD in the proposed alogliptin plus metformin FDC tablets, consistent with the proposed monotherapy and alogliptin plus pioglitazone FDC formulations in other NDAs.

2.6 Proposed Clinical Population and Dosing Regimen

Alogliptin plus metformin FDC immediate release (IR) tablets are indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Tablets are indicated for twice daily dosing based on the standard dosing regimen for immediate release metformin. (b) (4)

The pediatric development plan is similar to that proposed for alogliptin monotherapy and alogliptin plus pioglitazone FDC applications. A waiver was requested for pediatric trials for children aged 0 to 9 based on the small population with the disease at that age. A deferral of trials for children aged 10 to 17 was requested and the Sponsor proposed to utilize trials SYR-322_109 and SYR-322_309 discussed under NDAs 22-271 and 22-426 to address pediatric safety with alogliptin plus metformin FDC tablets². There are no substantive changes from the pediatric plan reviewed for prior alogliptin NDAs. Juvenile animal toxicology study reports have been submitted and reviewed previously and they are summarized and discussed in this review.³ No additional nonclinical studies are needed to support the proposed pediatric trials in 10 to 17 year old children.

2.7 Regulatory Background

Alogliptin drug substance has previously been recommended for approval by this Pharmacology/Toxicology reviewer for monotherapy and as alogliptin/pioglitazone FDC tablets. The metformin component of the proposed alogliptin/metformin FDC tablets is listed for marketing in the U.S.

3 Studies Submitted

3.1 Studies Reviewed

All studies reviewed in this or prior alogliptin NDA reviews.

3.2 Studies Not Reviewed

None.

¹ S. Markofsky, Personal Communication (see also CMC Review, pending).

² D. Carlson, Pharmacology/Toxicology Review and Evaluation, NDA 22-271, 1/18/12.

³ *IBID*.

3.3 Previous Reviews Referenced

Previous Pharmacology/Toxicology reviews of alogliptin monotherapy or FDC formulations are cited throughout this review, as appropriate.

4 Pharmacology

4.1 Primary Pharmacology

Alogliptin pharmacology has been described in prior pharmacology/toxicology reviews in NDA 22-271. Alogliptin is a member of the dipeptidyl peptidase IV (DPP4) inhibitor class of drugs. DPP4 is found in both membrane bound (cell-surface) and soluble (e.g. plasma) forms, with both forms inactivated by DPP4 inhibitor drugs. DPP4 inhibition has been shown to reduce blood sugar and glycated hemoglobin (HbA_{1c}) *in vivo* in healthy and diabetic animal models and in diabetic patients. Alogliptin is orally active and highly selective for DPP4 inhibition ($IC_{50} = 6.9$ nM) with no apparent inhibition of related dipeptidyl peptidase enzymes DPP2, DPP8, DPP9 or other serine peptidases ($IC_{50} > 100,000$ nM). Alogliptin has been shown to inhibit DPP4 enzymatic activity and lower blood glucose in a variety of *in vitro*, *ex vivo* (e.g. DPP4 plasma activity), and *in vivo* studies in healthy and diabetic animal models. Two main alogliptin metabolites, M-I (< 1% of parent) and M-II (4-6% parent), are found in human plasma. M-I potently inhibits DPP4 (calculated $IC_{50s} = 14-21$ nM) while M-II is inactive ($IC_{50} > 30,000$ nM). Neither metabolite is considered major (i.e., detected at <10% of parent compound) or relevant to the clinical glucose lowering activity of alogliptin.

DPP4 inactivates glucagon-like peptide 1 (GLP-1) by N-terminal cleavage. GLP-1 is an incretin hormone released from the L-cells in the gut after meals, which potentiates glucose-dependent insulin secretion from pancreatic β cells, leading to increased hepatic glucose metabolism. GLP-1 also suppresses glucagon secretion, which delays gastric emptying and independently contributes to reduced blood glucose concentrations. Inhibition of DPP4 by alogliptin prevents cleavage of GLP-1, prolonging its glucose-lowering effects on insulin secretion and glucagon suppression. There is some evidence that GLP-1 contributes to delayed progression of T2DM by slowing declines in β cell function which lead to the non-insulin-dependent diabetes characteristic of T2DM. DPP4 also rapidly inactivates another gut incretin, glucose-dependent insulintropic peptide (GIP). GIP enhances insulin secretion at GIP-specific receptors on β -cells, but unlike GLP-1 it does not affect gastric emptying, glucagon secretion, or appetite. In T2DM patients the GLP-1 response seems to be preserved more than the GIP-mediated effects. Thus, GLP-1 is considered to provide the major contribution to improved postprandial glucose and insulin homeostasis when DPP4 is inhibited.

Alogliptin and other DPP4 inhibitors are not expected to have any effect in the absence of a glucose load because the target incretin hormone GLP-1 is released after meals. In support of that hypothesis, alogliptin treatment did not increase plasma insulin or reduce

plasma glucose in fasted rats. Risks of hypoglycemic events due to DPP4 inhibition are expected to be lower than some diabetic therapies such as sulfonylureas or insulin, which do lower plasma glucose in fasted rats. Alogliptin did not inhibit intestinal sugar absorption in a fatty rat model, in contrast to metformin, which does inhibit intestinal sugar absorption.

DPP4 is also identified as the leukocyte antigen CD26 (membrane bound on T-cells) and it has additional substrates that, when DPP4 is inhibited, may contribute to glucose lowering effects or unexpected toxicity. DPP4 substrates include neuropeptides (e.g. neuropeptide Y, substance P), growth factors (e.g. growth hormone releasing hormone (GRH)), and various chemokines. Inhibition of DPP4 could lead to side effects related to immune function, chemotaxis, and cell growth.

Metformin pharmacology is still not entirely understood but it seems to improve insulin sensitivity at peripheral target tissues including liver, muscle, and adipose. Metformin does not seem to directly affect insulin production or metabolism, but treatment increases glucose uptake and utilization in peripheral tissues, decreases hepatic glucose production, and decreases intestinal glucose absorption. Metformin inhibits hepatic gluconeogenesis and glycogenolysis while stimulating glycogen synthase (and thus glycogen synthesis) and altering membrane glucose transporters. Metformin treatment results in both basal and postprandial plasma glucose reductions in T2DM patients.

The complementary mechanisms for alogliptin- and metformin-induced glucose lowering are expected to result in improved therapeutic benefit when given together to diabetic patients. Clinical data show metformin treatment increases plasma GLP-1, with or without concomitant DPP4 inhibitor treatment, likely by stimulating GLP-1 secretion rather than GLP-1 breakdown. Pivotal clinical trials with alogliptin and metformin coadministration and with the FDC tablet showed approximately additive effects on HbA_{1c} lowering compared to either drug alone. In addition, treatment with alogliptin plus metformin improved plasma glucose status as measured by HbA_{1c} when given on a background of pioglitazone treatment (a thiazolidinedione).

4.2 Secondary Pharmacology

Combination alogliptin plus metformin studies were conducted *in vivo* to assess drug interactions related to mechanisms of improved glucose tolerance. Studies were reviewed in NDA 22-271 and summaries are reproduced here.

Effect of alogliptin and metformin on intestinal xylose absorption (Study SD1AD2007-KT-184)

Non-GLP (research study), signed 4/3/08

Summary: Intestinal xylose absorption was investigated in Wistar fatty (WF) rats to determine if the plasma glucose lowering mechanism of alogliptin or metformin may involve decreased glucose absorption. A single 1 mg/kg oral alogliptin dose had no

effect on xylose absorption, whereas ≥ 50 mg/kg metformin decreased xylose absorption by $\geq 14\%$ (ss) compared to vehicle (0.5% methylcellulose) controls. Intestinal sugar absorption occurs primarily through sodium glucose cotransporter 1 (SGLT1) and is not insulin-dependent (confirmed by the SGLT inhibitor positive control, phlorizin). Results suggest improved glucose tolerance after combination alogliptin plus metformin in WF rats may involve independent and/or complementary mechanisms.

Effect of alogliptin and metformin on glucose tolerance and GLP-1 (Study SYAD2009-KT-024)

Non-GLP (research study), signed 11/9/09

Summary: Female Wistar fatty (WF) rats were treated orally with vehicle (0.5% methylcellulose), 3 mg/kg alogliptin, 50 mg/kg metformin, or alogliptin (3 mg/kg) plus metformin (50 mg/kg). Plasma glucose, plasma insulin, and plasma active GLP-1 were measured in fasted animals for 2 h after a glucose load (i.e., oral glucose tolerance test (OGTT) given 60 min post-dose). Results were also compared to non-diabetic Wistar lean (WL) rats treated with vehicle. The alogliptin plus metformin combination improved the glucose response to OGTT in an additive manner (ss 27% decreased AUC vs. 12-13% for monotherapies) and improved GLP-1 activity in a synergistic manner (ss 20-fold increased activity vs. 7-fold for alogliptin alone). Combination treatment did not increase plasma insulin levels, rather, alogliptin alone had the largest effect on plasma insulin.

Effect of alogliptin, metformin, and pioglitazone combination on glucose tolerance (Study SD1AD2007-KT-124)

Non-GLP (research study), signed 3/25/08

Summary: Male Wistar fatty (WF) rats were pre-treated (6 d) with 1 mg/kg pioglitazone (or vehicle) and response to oral glucose tolerance test (OGTT) was assessed after 1 mg/kg alogliptin and 50 mg/kg metformin alone or in combination. Triple combination of drugs improved glucose excursion as decreased $AUC_{0-120 \text{ min}}$ by 55% compared to 37-38% decrease by combination pio + alo, pio + met, or alo + met. As expected, alogliptin increased plasma active GLP-1, while metformin slightly increased active GLP-1 and a supra-additive increase in active GLP-1 was observed with alo + met combination (consistent with a separate study). Alogliptin treatment did not further improve insulin response from pioglitazone $\pm$ metformin treatment.

5 Pharmacokinetics/ADME/Toxicokinetics

5.2 Toxicokinetics

A combination alogliptin plus metformin single oral dose TK study was conducted in rats, reviewed in NDA 22-271, and the summary is reproduced here.

Single combination oral gavage alogliptin + metformin rat TK (Study 08-329/tk)
Non-GLP range-finding, signed 3/3/09

Summary: Alogliptin and metformin were coadministered by oral gavage to SD rats (n=2/sex/group) at doses of 100/0, 0/100, 0/300, 0/1000, 100/1000 mg/kg alogliptin/metformin. Maximum (C_{max}) and total (AUC_{0-24h}) metformin exposure increased with increasing dose and exposure was not affected by alogliptin coadministration. Both C_{max} and AUC_{0-24h} of alogliptin were decreased, generally 2-fold or more, with HD metformin coadministration compared to alogliptin alone. Alogliptin metabolite M-I and M-II exposures were also lower with metformin coadministration.

6 General Toxicology

Toxicity studies with the components of FDC drugs are typically required to provide a “bridge” to results seen with the individual components and to investigate any potential additive or synergistic toxicity. Coadministration of alogliptin and metformin were investigated in 4 week dose-ranging and pivotal 13 week toxicity studies in rats. Rats were considered an adequate species because non-rodent species were not apparently more sensitive to toxicity from either drug. Studies were previously reviewed under NDA 22-271⁴ but tabular summaries from the original review are provided here because the studies are pivotal to assess safety of the alogliptin/metformin FDC tablet.

6.2 Repeat-Dose Toxicity

Four week dose-ranging alogliptin + metformin study in rats

Non-GLP, signed 5/25/09 (Study No. 08-332/su, Report No. SYR-322MET-10012)

0, 30/0, 100/0, 30/100, 100/100, 100/300, 100/1000 mg/kg alogliptin/metformin
5/0, 25/0, 7/30, 30/32, 29/100, 25/265 $\mu\text{g}\cdot\text{h}/\text{ml}$ alogliptin/metformin

NOAEL = 30/100 mg/kg alogliptin/metformin (5X alo / 1X met MRHD)

Summary: Isolated, low incidence and low severity findings were seen in kidney (hyaline droplets) and adrenal gland (increased weight) in 30/100 alo + met combination, which were not considered adverse in the absence of other signs of toxicity. Signs of modest toxicity in kidney (tubule hyaline droplets or vacuolation), heart (cardiomyopathy), and submandibular gland (decreased duct granules) were more evident at 100/100 and 100/300 combinations. The HD 100/1000 mg/kg combination dose showed clearly increased incidence and severity of toxicity in multiple target organs.

Key Study Findings:

- Kidney hyaline droplets and/or vacuolization in renal tubules in all groups, tubular basophilia in females $\geq$ 100/100 mg/kg group, with increased incidence and/or severity in 100/1000 mg/kg HD. Biological significance was unclear.⁵
- Submandibular gland minimal decreased granules (in granule ducts) in males $\geq$ 100/300 and male duct wall hypertrophy and female duct hypertrophy in 100/1000 HD combination.
 - Sublingual gland minimal duct hypertrophy in HD combo females

⁴ D. Carlson, Pharmacology/Toxicology Review and Evaluation, NDA 22-271, 1/18/12

⁵ Reviewer's note – analyses in the 13-week study identified $\alpha_2\mu$ -globulin in males, presumably in phagolysosomes, and lipid droplets in females at $\geq$ 100/100 mg/kg alo/met

- More pronounced toxicity evident in HD combination 100/1000
 - Modest clinical signs– salivation, loose stool, crystalluria, soiled fur
 - ↓ Body weight gain (♂) and ↓ food consumption
 - ↑ Lactic acid
 - ↑ Triglycerides
 - Target organ toxicity (↑ liver (+30-40%), heart (+25-30%), ovary (+30%) and adrenal gland (+11-32%) weights; minimal centrilobular hepatocyte hypertrophy (♀); mild cardiomyopathy; and kidney tubule hyaline droplets, vacuolization, and/or basophilia.
- No clear treatment-related ophthalmoscopy, hematology, or gross pathology findings

Thirteen week combination alogliptin + metformin study in rats

GLP statement, signed 1/13/10

Doses 0/0 (vehicle control)
(mg/kg/d) 100/300, 100/1000 mg/kg (Alogliptin / Metformin)
 0/300, 0/1000 mg/kg (metformin LD & HD controls)

Exposures: 47/110, 34/242, 0/84, 0/230 µg*h/ml (alogliptin / metformin)

NOAEL < 100/300 alogliptin / metformin (31X alo / 4X MRHD)

NOAEL determination – toxicity was largely due to metformin with additive effects of alogliptin on some targets. Low doses of metformin ± alogliptin were tolerated but not without toxicity, while higher doses of metformin ± alogliptin caused more marked toxicity (including death of one male). The study was designed to identify potential unexpected toxicity from combined alogliptin and metformin treatment. No unusual synergistic interactions were observed. Combination treatment resulted in toxicity predicted by the individual drugs and the absence of a NOAEL did not affect interpretation of the study results.

Key Study Findings:

- Slight additive effects of alogliptin on certain metformin-induced toxicity were observed but there was no evidence of a synergistic effect of combination
 - Toxicity was generally not worsened by alogliptin coadministration
 - Difficult to make definitive conclusions about alogliptin-related toxicity because of the absence of any alogliptin only controls
- Metformin-induced toxicity included reduced BW gain, plasma lactic acid accumulation without concomitant increased bicarbonate, increased serum ALT and CK, slight alterations in plasma electrolytes, increased organ weights (heart, liver, kidney, salivary gland, adrenals), and correlative histological lesions.
- Target organs were heart, kidney, liver, and salivary and adrenal glands. Heart cardiomyopathy and myocardial hypertrophy, liver hepatocyte hypertrophy, kidney tubule regeneration and hypertrophy, salivary gland hypertrophy, and adrenal

vacuolation and hypertrophy were correlated with organ/tissue weight increases. GI tract was also a target based on stomach gross foci and erosion, duodenum erosion, and cecum hyperplasia.

- Kidney tubules had increased vacuolation and/or droplets, identified as hyaline droplets (possibly $\alpha_2\mu$ -globulin-containing phagolysosomes) in males and lipid accumulation in females.
- Metformin C_{max} , but not AUC, was decreased 25-30% with alogliptin coadministration. Alogliptin C_{max} and AUC decreased slightly, approximately 25-40%, with increasing metformin coadministration. Alogliptin exposure was approximately 2-fold higher on day 90 than day 1, and male exposures were approximately 20-30% lower than females. Alogliptin metabolite exposure to M- was 10-15% of parent and 2-3% of parent for M-II, consistent with treatment with alogliptin alone in separate studies.

7 Genetic Toxicology

Genetic toxicity of alogliptin and metformin were assessed individually to support the safe use of each monotherapy. Neither alogliptin nor metformin were found to have genotoxic potential. Alogliptin genotoxicity studies were reviewed under the monotherapy application, NDA 22-271.⁶ Results of metformin genetic toxicity studies are described in the Glucophage® label.

8 Carcinogenicity

Carcinogenic potential was previously assessed in lifetime rat and mouse bioassays for alogliptin and metformin. Alogliptin carcinogenic potential was discussed under the monotherapy application, NDA 22-271.⁷ Results of metformin carcinogenicity studies are described in the Glucophage® label. No potential interactions were uncovered in combination toxicity studies to suggest altered or additional carcinogenic potential.

9 Reproductive and Developmental Toxicology

A combination alogliptin plus metformin study was required by the Division to investigate possible DPP4 inhibitor class-related effects on rat embryofetal development when coadministered with metformin. Studies were conducted by the Sponsor and reviewed under NDA 22-271.⁸ Because the studies are pivotal to the alogliptin/metformin FDC tablet tabular summaries of the study reviews are provided here.

9.2 Embryonic Fetal Development

Range-finding alogliptin + metformin combination embryofetal rat study

Non-GLP, signed 8/6/10

Study Title: Range-finding study for effects of SYR-322/metformin hydrochloride on embryo-fetal development in rats (Study No. 09-160/te; Doc. No. SYR-322MET-11134)

Doses 0/0 (vehicle control)
(mg/kg/d) 100/50, 100/150, 100/500, 100/1000, 100/2000 (Alogliptin / Metformin)

NOAEL (maternal) = 100/150 (Alogliptin / Metformin)

NOAEL (fetal) = 100/150 (Alogliptin / Metformin)

⁶ D. Carlson, Pharmacology/Toxicology Review and Evaluation, NDA 22-271, 8/27/08

⁷ *IBID*

⁸ D. Carlson, Pharmacology/Toxicology Review and Evaluation, NDA 22-271, 1/18/12

NOAEL determination – Metformin doses ≥ 500 mg/kg plus alogliptin caused decreased maternal BW gain during the treatment period. Toxicity in dams treated with ≥ 1000 mg/kg metformin exceeded the MTD, including moribund sacrifice and death, clinical signs (abnormal feces, vaginal discharge in survivors), and limited BW gain until the post-treatment period.

Key study findings:

- Oral gavage range-finding study of alogliptin + metformin coadministration to pregnant rats (n=6/group). Increasing doses of metformin (50 to 2000 mg/kg) coadministered to fixed 100 mg/kg alogliptin dose. Doses of metformin ≥ 1000 mg/kg plus alogliptin were not well tolerated as evidenced by markedly reduced BW gain, abnormal clinical signs, and death or moribund sacrifice of dams.
- Transient decreased BW gain and decreased food consumption with 500 mg/kg metformin plus alogliptin, leading to overall 20% decreased BW gain during treatment with rapid compensatory weight gain post-treatment.
- Signs of lactic acidosis in 2000 mg/kg metformin dams sacrificed in moribund condition included increased lactic acid, decreased bicarbonate ion (HCO_3^-), and increased anion gap.
- There was no apparent effect on pregnancy success or fetal development with up to 1000 mg/kg metformin plus alogliptin treatment. No fetal malformations were observed but skeletal variations seemed to increase with ≥ 500 mg/kg metformin treatment ($\uparrow$ total skeletal variations (nss), $\uparrow$ bipartite ossification thoracic centrum (nss), $\uparrow$ short supernumerary rib (nss), $\downarrow$ number of ossified sacro-caudal vertebrae (ss)).

Alogliptin + metformin combination embryofetal rat study (Seg 2 rat)

GLP study, signed 9/16/10

Doses 0/0 (vehicle control)
 (mg/kg/d) 100/150, 100/500 (Alogliptin / Metformin)
 100/0 (Alogliptin only control)
 0/150, 0/500 (Metformin only controls)

Exposures: 51 / 70, 35 / 163 (alogliptin / met GD 17)
 ($\mu\text{g}\cdot\text{h}/\text{ml}$) 44 / 0 (alogliptin)
 0 / 40, 0 / 149 (LD and HD metformin)

NOAEL (maternal) = 100 / 150 mg/kg (Alogliptin / Metformin) (34X alo / 3X MRHD)

NOAEL (fetal) = 100 / 150 (Alogliptin / Metformin) (no exposure data)

NOAEL determination – No treatment-related fetal findings were seen in metformin controls or in 100/150 mg/kg alogliptin/metformin dams. The high dose of 100/500 mg/kg alogliptin/metformin caused reduced maternal body weight and eye and vertebral malformations in 4 fetuses from 2/20 dams. A relationship to treatment could not be ruled out for deformed fetuses, but findings were limited to microphthalmia in fetuses from a dam with markedly reduced BW gain and a single fetus with multiple abnormalities in a separate dam.

Key study findings:

- There was no evidence of an unexpected, synergistic increase in embryofetal toxicity with alogliptin and metformin coadministration.
- Transient reduced BW gain and reduced food consumption at the beginning of treatment led to overall reduced BW gain in HD combination dams (↓ 13%) indicating maternal toxicity.
- A single HD combination dam had 3 fetuses with microphthalmia and 1 fetus with absent sacral vertebrae malformations. The dam had markedly reduced BW gain compared to other dams in the HD combination group and compared to controls, suggestive of marked maternal toxicity.
- A single HD combination fetus (from a different dam) had several malformations: microphthalmia, cleft palate, microglossia, and mandibular micrognathia.
- There were no other treatment-related malformations and no apparent treatment-related external, visceral, or skeletal variations.
- There were no apparent treatment-related effects on pregnancy success or other pregnancy-related or fetal outcomes.
- Fetal exposure was not measured but maternal transfer to developing fetuses has been previously established for alogliptin and metformin.

9.4 Juvenile Development

The Sponsor conducted two juvenile animal studies with alogliptin. The studies, a general 4-week study in males and females and a separate 8-week study investigating male reproductive system development, were reviewed under NDA 22-271.⁹ As noted in the prior review, juvenile animal studies were not required by the Division and no rationale for the studies was provided, but they may have been prompted by male reproductive tissue toxicity at high doses in chronic toxicity studies.

No effects on growth and development of juvenile rats were observed up to the highest dose tested in males and females treated for 4 weeks (300 mg/kg, 77X MRHD) or in males treated for 8 weeks (300 mg/kg, 88X MRHD). Juvenile animal data confirmed short-term toxicity profiles were similar in juveniles and adults but did not address potential alogliptin effects on pubertal onset, behavioral development, or fertility. No drug-related effects on male reproductive system growth and development were observed.

11 Integrated Summary and Safety Evaluation

The proposed alogliptin/metformin FDC tablet (KazanoTM – proposed) was submitted in accordance with 21 USC 505(b)(2) for treatment of type 2 diabetes mellitus as an adjunct to diet and exercise. All pivotal studies were conducted in compliance with current GLP standards. The Sponsor also included references to peer-reviewed literature and public data on metformin to support its use in the FDC tablet formulation.

Pharmacology

Pharmacology studies relevant to alogliptin plus metformin FDC tablets were submitted and reviewed in NDA 22-271. Metformin, but not alogliptin, slowed intestinal sugar absorption, suggesting improved glucose tolerance in diabetic rats (Wistar Fatty) may involve independent and/or complementary mechanisms of alogliptin and metformin. Results were consistent with improved clinical glucose control with alogliptin treatment on background metformin therapy. When diabetic rats (Wistar Fatty) were pre-treated with pioglitazone followed by alogliptin plus metformin, glucose excursion was improved compared to treatment with dual combination treatments (pio + alo, pio + met, or alo + met). Triple combination treatment resulted in maximal effects on active plasma GLP-1 but did not further improve insulin response expected from pioglitazone ± metformin. Combination alogliptin plus sulfonylurea (glibenclamide) treatment in another diabetic rat model (N-STZ-1.5) also showed additive improvement in glucose excursion and insulin secretion, with earlier maximum insulin response, compared to individual drugs alone.

⁹ *IBID.*

Toxicology

Toxicology studies were submitted to support safe use of alogliptin coadministered with metformin. The GLP studies focused on alogliptin and metformin combination treatment in healthy rats (13-week combination toxicity study) and pregnant rats (combination embryofetal development study), and alogliptin treatment in juvenile rats (general juvenile growth study and male reproductive system development study). All of the studies were previously submitted and reviewed for NDA 22-271, due to expected widespread use of alogliptin on a background of metformin treatment (i.e., drug coadministration compared to administration as a FDC tablet).

Toxicity study reviews were summarized above. Discussion and conclusions from the original NDA reviews are reproduced here:¹⁰

“There was no unexpected toxicity and no apparent synergistic increase in toxicity in combination alogliptin and metformin studies in rats. Toxicity was generally driven by metformin treatment due to lower metformin exposure margins at the respective MTDs for alogliptin and metformin in rats. Toxicity studies were designed to identify additive or synergistic effects of well tolerated alogliptin doses in combination with MTD metformin doses.

A standard three month rat alogliptin plus metformin toxicity study showed slight additive effects of alogliptin on certain metformin-induced toxicity but toxicity was generally not worsened by combination treatment. There was no evidence of a synergistic effect of alogliptin and metformin combination treatment but the absence of an alogliptin only control made interpretation of any alogliptin-induced toxicity difficult. Consistent with predicted effects, metformin-induced toxicity included reduced BW gain, plasma lactic acid accumulation without concomitant increased bicarbonate, increased serum ALT and CK, slight alterations in plasma electrolytes, and increased organ weights (heart, liver, kidney, salivary gland, adrenals) with correlative histological lesions. Heart cardiomyopathy and myocardial hypertrophy, liver hepatocyte hypertrophy, kidney tubule regeneration and hypertrophy, salivary gland hypertrophy, and adrenal vacuolation and hypertrophy were correlated with organ/tissue weight increases. GI tract was also a target based on stomach gross foci and erosion, duodenum erosion, and cecum hyperplasia. Alogliptin exposure (C_{max} and $AUC_{0-24\ h}$) decreased slightly, approximately 25-40% with increasing metformin coadministration. Metformin co-treatment did not affect alogliptin metabolism.

DMEP required a combination alogliptin plus metformin rat embryofetal development study with ... because of potential class-related effects of DPP4 inhibitors and metformin. There were no treatment related fetal findings in

¹⁰ D. Carlson, Pharmacology/Toxicology Review and Evaluation, NDA 22-271 (8/27/08 and 1/18/12)

alogliptin or metformin controls or in the low dose combination treatment (34X alogliptin/ 3X metformin MRHD). In the high dose combination treatment group there was evidence of maternal toxicity based on reduced BW gain. Eye and vertebral malformations were seen in 4 fetuses from 2 (of 20) dams in the HD combination (23X alogliptin/ 6X metformin MRHD). A relationship to treatment could not be ruled out for deformed fetuses, but findings were limited to microphthalmia in three fetuses from one dam with markedly reduced BW gain and a single fetus (microphthalmia, cleft palate, microglossia, and mandibular micrognathia) with multiple abnormalities in a separate dam. There were no other treatment-related malformations and no apparent treatment-related external, visceral, or skeletal variations. There were no apparent treatment-related effects on pregnancy success or other pregnancy-related or fetal outcomes in any group. With the exception of fetal malformations from two HD combination dams but none in dams treated only with alogliptin or metformin, there was no clear evidence of unexpected or synergistic increase in maternal or embryofetal toxicity.

Juvenile toxicity studies have not been required for the DPP4 inhibitor class prior to conducting pediatric clinical trials, based on the absence of a clearly increased risk of children and adolescents to treatment. Pediatric trials had not been planned ... and juvenile toxicity studies were not required by DMEP prior to...[NDA 203-414 submission]. However, evidence of alogliptin-induced testicular toxicity at high multiples of expected clinical exposures in monkeys (>30X) and rats (>200X) suggested potential risk to developing male reproductive system in male children. The Sponsor conducted and submitted separate studies in juvenile male and female rats and a longer duration study dedicated to male reproductive system development in rats. There was no evidence of alogliptin-induced toxicity in male and female rats treated from age 4-weeks to age 8-weeks with up to 77-times expected clinical exposures. In the dedicated male reproductive system development study, male rats treated from age 4 weeks to age 12 weeks had no apparent general toxicity or any effects on male reproductive system growth and development at up to 88-times expected clinical exposures.

While results of the juvenile animal studies suggest a similar toxicity profile in adults and juveniles after short term exposures, there are several issues that limit conclusions about juvenile and/or male reproductive toxicity. The Sponsor provided no rationale for the conduct and design of juvenile animal studies and there were no discussions with DMEP pharmacology/toxicology about study endpoints. The combined sex study was a short duration, limited to 4 weeks of treatment, and lacked standard endpoints such as pubertal onset, behavioral maturation, and fertility. Similarly, the dedicated juvenile male study was limited to treatment post-weaning and to standard toxicity assessment of male reproductive tissues (e.g., organ weight, gross pathology, histopathology) but did not directly assess sperm development (e.g., sperm morphology and motility) or male fertility. As conducted, study

results did not identify any clear risk to alogliptin exposure in juvenile rats. Considering high exposure multiples in juvenile animal studies and absence of findings in standard reproductive and developmental toxicity studies (male and female fertility and early embryonic development, embryofetal development, pre- and post-natal development), risks to developing animals are considered minimal.”

Alogliptin target organ summary

- **Kidney** (≥ 32X MRHD at NOAEL; > 200X MRHD at LOAEL in chronic studies)
 - Rat: mortality, tubular degeneration/regeneration, transitional cell hyperplasia, increased female chronic progressive nephropathy background disease rate (~50% background incidence)
 - Rabbit: mortality
- **Lung** (≥ 32X MRHD at NOAEL; > 200X MRHD at LOAEL in chronic studies)
 - Rat: gross discoloration and focus/foci, histological histiocytosis
- **Liver** (≥ 32X MRHD at NOAEL; > 200X MRHD at LOAEL in chronic studies)
 - Rat: hypertrophy, periportal vacuolation, basophilic ‘focus of cell alteration’
- **Testes** (≥ 32X MRHD at NOAEL; > 200X MRHD at LOAEL)
 - Rat: testes atrophy/degeneration, small seminal vesicles, oligospermia and abnormal sperm, epididymids germ cell debris
 - Monkey: possible, unconfirmed decreased testes weight
- **Urinary bladder** (≥ 32X MRHD at NOAEL; > 200X MRHD at LOAEL)
 - Rat: gross calculus/calculi, simple transitional cell hyperplasia, treatment-related mortality
- **Immune/skin** (hypersensitivity/pseudoallergy) (~10-20X MRHD at NOAEL; ~20-30X MRHD at LOAEL)
 - Dog: flushing, swelling, hypersensitivity/pseudoallergy (as early as single dose)
 - No skin lesions any species
 - No phototoxicity

12 Appendix/Attachments

Table 2 – Tabulated summary of alogliptin + metformin toxicity studies

Toxicity Studies in Rat			
Study	NOAEL	MRHD Multiple ^a	Findings
13-Week Combo. Tox. GLP (#B-6610) Alogliptin / Metformin 100/300, 100/1000 0/300, 0/1000 mg/kg 47/110, 34/242 0/84, 0/230 µg*h/ml	< 100/300 mg/kg	< 31X Alo / 4X Met	Slight additive effect of alogliptin on metformin-induced toxicity Metformin toxicity: ↓ BW gain, ↑ lactic acid, ↑ ALT, ↑ CK, ↑ organ weights (heart, liver, kidney, sal. gland, adrenals), cardiomyopathy + myocardial hypertrophy, hepatocyte hypertrophy, kidney tubule regen./hypertrophy, sal. gland hypertrophy, adrenal vacuolation & hypertrophy
Embryofetal Develop. GLP (#09-260/TE) Alogliptin / Metformin 100/150, 100/500, 100/0, 0/150, 0/500 51/70, 35/163, 44/0, 0/40, 0/149 µg*h/ml	100/150 mg/kg (Maternal & Fetal)	34X Alo/ 3X Met	No synergistic toxicity 100/500 – maternal toxicity (↓ BW gain; fetal malformations (2 dams, 4 fetuses) – microphthalmia, etc.; no fetal variations or pregnancy effects
Juvenile tox. (alogliptin) 4-Week (♂ & ♀) GLP (#B-6504) 30, 100, 300 mg/kg 5, 27, 115 µg*h/ml	300 mg/kg	77X Alo	No treatment-related findings Did not evaluate pubertal onset, behavioral development, or fertility
Juvenile tox. (alogliptin) 8-Wk ♂ Repro. organs GLP (#B-6812) 30, 100, 300 mg/kg 7, 38, 132 µg*h/ml	300 mg/kg	88X Alo	No treatment-related findings Did not evaluate sperm development (morphology/motility), fertility, or mating

^a Exposure multiple estimates based on daily MRHD clinical exposures from 25 mg alogliptin ($AUC_{0-24\text{ h}} = 1.5 \mu\text{g}^*\text{h/ml}$) and 2000 mg metformin ($AUC_{0-24\text{ h}} = 26 \mu\text{g}^*\text{h/ml}$)

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/s/

DAVID B CARLSON
07/23/2012
PharmTox Approval Recommendation

TODD M BOURCIER
07/23/2012
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203-414

Applicant: Takeda

Stamp Date: November 22,
2011

Drug Name: Alogliptin +
metformin FDC

NDA/BLA Type: 505(b)(2)

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Combination embryofetal rat studies submitted. No other special requests.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			Labeling will need to be updated to be consistent with final alogliptin monotherapy and updated metformin labels.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No impurity issues identified during development. Drug substances have been previously reviewed. Final drug product is new – Sponsor statement that no novel excipients used in drug product.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION
FILEABLE?** Yes

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

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

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID B CARLSON

01/10/2012

PharmTox -- NDA is fileable

TODD M BOURCIER

01/11/2012

I concur