Clinical Study Report

Efficacy and tolerability of prolonged-release metformin (XR) in diabetic subjects in stages 1 and 3B of chronic kidney disease

EudraCT number: 2016-001233-27
Sponsor code: PI2016_843_0008
NCT02895750

Version n°1.0, dated 19/02/2021

Sponsor:
CHU Amiens-Picardie
Place Victor Pauchet
80054 AMIENS Cedex 1

Principal Investigator:
Jean-Daniel LALAU, CHU Amiens-Picardie
Service d'endocrinologie, maladies métaboliques et nutrition
Site Nord
Place Victor Pauchet
80054 AMIENS Cedex 1

CONFIDENTIAL

Signature page for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: Date: ____/____/_____

Print name: Anne PARIS

Affiliation: Directrice des Affaires Médicales, de la Recherche et de l'Innovation

Address: CHU Amiens-Picardie, 80054 Amiens Cedex 1, France

Signed: Date: ____/____/_____

Print name: Jean-Daniel LALAU

Affiliation: Service d'endocrinologie, maladies métaboliques et nutrition

Address: CHU Amiens-Picardie, 80054 Amiens Cedex 1, France

1 TITLE PAGE

Study title: Efficacity and safety of metformin XR in CKD stage 1 to 3B (METXR/CKD)

Study number: EudraCT number: 2016-001233-27

Name of Test Drug: Metformin XR

Indication studied: Type 2 diabetes patients

Clinical Phase: II

Investigators/study centres: Single center CHU Amiens-Picardie; investigator: Prof. Jean-Daniel Lalau

Sponsors: CHU Amiens-Picardie, 80054 Amiens Cedex 1

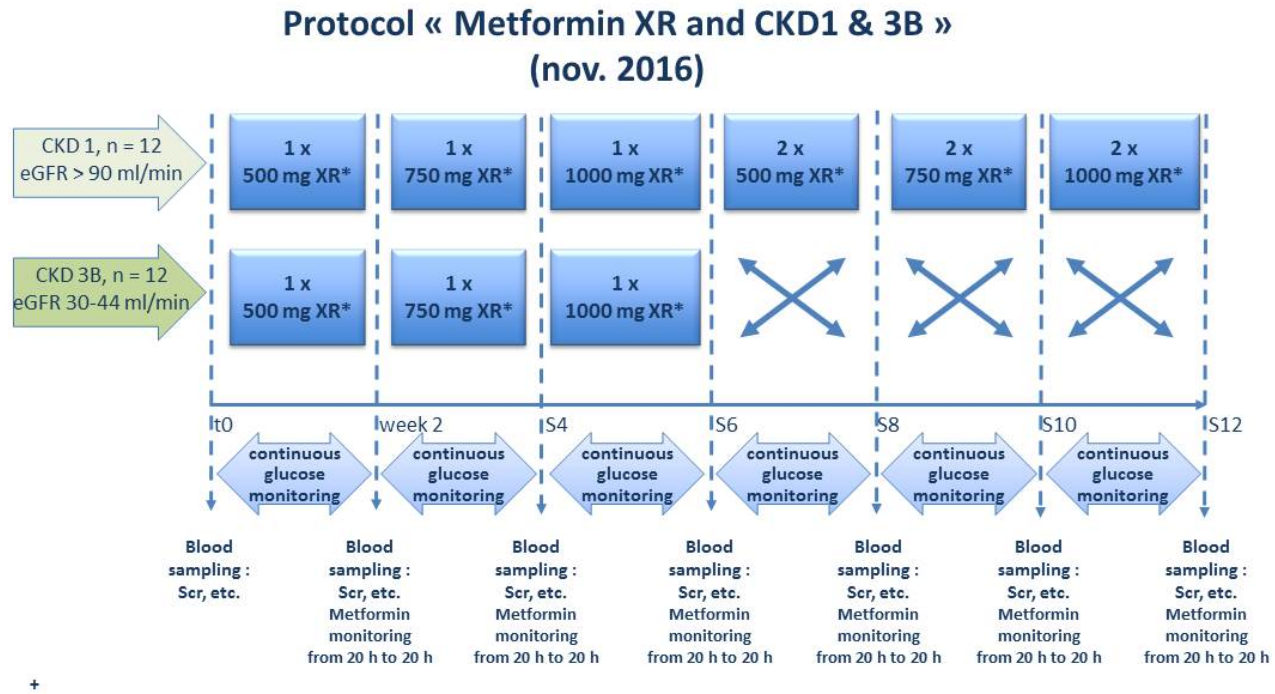
Medical Officer: Prof. Jean-Daniel Lalau, Service d'Endocrinologie-Nutrition, CHU Amiens-Picardie, Hôpital Nord, Place Victor Pauchet, 80054 AMIENS Cedex. FRANCE

Sponsor signatory:

Madame Anne PARIS
Directrice des Affaires Médicales, de la Recherche et de l'Innovation

GCP Statement: This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents

2 SYNOPSIS

Study title	**Efficacity and safety of metformin XR in CKD stage 1 to 3B (METXR/CKD)**
Principal Investigator	Prof. Jean-Daniel Lalau, Service d'Endocrinologie-Nutrition, CHU Amiens-Picardie, Hôpital Nord, Place Victor Pauchet, 80054 AMIENS Cedex. FRANCE
Study phase	Phase II: - Metformin XR not marketed in France;
Study center(s)/country (ies)	Single Center Study: Service d'Endocrinologie-Nutrition, CHU d'Amiens, Hôpital Nord, Place Victor Pauchet, 80054 AMIENS Cedex 1. FRANCE
Planned study period	2016-2017
Executed study period	2019-2020
Study Rationale	There is limited data availability on effect of Metformin XR on 24-hours plasma glucose, and there is no available data in chronic kidney disease (CKD). The planned study aims to provide data on glucose plasma level in relation to metformin plasma level in Diabetes Type II patients.
Study objectives	Primary: To exhibit the efficacy of once daily Metformin XR on 24-hours blood glucose control. Secondary: To exhibit the tolerability of Metformin XR in mild to moderate (CKD).
Study design Non-randomized, uncontrolled, open-label, single-center pilot study:  The blood glucose will be measured continuously throughout the study using CGMS. Creatinine and lactate levels will be measured at the end of each block.	
Planned number of subjects	24 subjects: - Arm 1 (12 subjects): eGFR ≥ 90 (normal renal function, CKD stages 1) - Arm 2 (12 subjects): eGFR 44-30 (moderate to severe renal impairment, CKD stage 3B)

Diagnosis and main criteria for inclusion	Type 2 diabetes patients (diagnosed diabetic at least for 6 months) aged between 18 and 80 years, requiring metformin (and any other antidiabetic treatment)
Diagnosis and main criteria for exclusion	- Pregnancy and lactation - Hyperlactatemia (> 2.5 mmol/L) - No creatinine levels available since 3 months - Severe hepatic insufficiency - No liver function parameters available - Need of investigation with iodized contrast media - Hypersensitivity to metformin
Study medication	Metformin
Reference drug dose and treatment duration	- Metformin extended release tablets (Glucophage 500 mg; 750 mg; 1,000 mg). - 6 weeks (CKD 3B)
Hypothesis	Primary - The once daily dosing of metformin extended release is effective on blood glucose control. - There is an equivalence of metformin XR effect on blood glucose of 500mg (2 tablets) versus 1000 mg (one tablet) (in CKD 1). - Metformin XR is equally effective on post-prandial and fasting glucose. Secondary - Tolerability of Metformin XR in moderate CKD (i.e. without occurrence of hyperlactatemia).
Primary target variable	- 2 week-blood glucose control (mean, range, and variability per treatment block) - Pharmacokinetic parameters (AUC, …)
Secondary target variables	- Lactate levels
Statistical analysis (incl. statistical tests, significance level, sample size calculation)	Per patient: - Interdosage comparisons of study parameters (ANOVA) Per dosage: - Interarm comparisons of study parameters (ANOVA). Per arm: - Interblock comparisons of study parameters (t-test and ANOVA).

TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS & DEFINITION OF TERMS

AUC: Area under the curve
CGMS: Continuous glucose monitoring system
GFR: Glomerular filtration rate
XR: Extended release
IR: Immediate release
CKD: Chronic kidney disease
γGT: Gamma glutamyl transpeptidases
ASAT: Aspartate aminotransferase
ALAT: Alanine aminotransferase
HbA1c: Glycated hemoglobin
MDRD: Modification of diet in renal disease

4 ETHICS AND REGULATORY APPROVAL

This research received the favorable opinion of the Committee of Protection of Persons (CPP) Nord-Ouest II dated 03/11/2016 and the authorization of the ANSM dated 31/08/2016.

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6 INTRODUCTION

6.1 RATIONALE FOR THE STUDY

The European Medicines Agency successively raised the contraindication of metformin in renal insufficiency in stage 3A (ref 6) and in stage 3B (new ref. 7). Concerning the metformin extended Release (XR), a galenic formulation allowing once-day dosing, pharmacokinetic clinical studies have been performed, but in healthy subjects [2]); No prospective clinical data exist in patients renal insufficiency to date, let alone a joint study on the dose dependent effect (on blood glucose), pharmacokinetics (AUC, etc.), and metabolic tolerance (lactatemia).

CURRENT STATUS OF KNOWLEDGE

PATHOLOGY

It has been estimated that more than 10% of the adult population in developed countries have chronic renal failure (CKD), with an incidence increasing each year by 8%. Diabetes and high blood pressure are the two main causes and diabetes is the main cause of terminal CKD. The human and societal cost is considerable; It accounts for about 2% of total health expenditure [3, 4].

TREATMENTS REFERENCE

The strategy of dose adjustment according to renal function has already been validated by our previous studies in the elderly [5]. This strategy is being validated in a new study carried out this time in the diabetic patient aged 18 to 80 years (EudraCT: 2012-001207-20), a two-stage study: a short-term study carried out at all stages of IRC (1 to 5), with a progressive dosage of metformin and partial results published [1]; And a follow-up study of 4 months in stages 3a, 3b and 4 of chronic renal insufficiency, this time with a fixed dose of metformin (1.5 g, 1 g, and 0.5 G / day).

This complementary study is being completed with a pharmacokinetic study in a subgroup of patients. Our preliminary results show a good tolerance of metformin even in severe chronic renal failure (stage 4 of chronic renal insufficiency), but at a dose of metformin greatly reduced: 0.5 g / day.

Although our knowledge is progressing on the classic galenic formulation of metformin, there are no prospective pharmacokinetic studies to date on metformin extended release (XR) in chronic renal insufficiency. Thus, the present study proposed to treat diabetic patients with once-daily oral metformin XR for a period of 12 weeks for stage 1 of CKD (with a creatinine clearance higher than 91 ml / min / 1.73 m^2) or 6 weeks for stage 3B of CKD (creatinine clearance from 44 to 30 ml / min / 1.73 m^2).

6.2 Research hypotheses and expected results

Principal hypothesis:

- Single intake of the appropriate dose of metformin XR is effective on glycemic control;
- There is an equivalent effect on glycemia of 2 tablets of metformin XR at 500 mg and 1 tablet at 1 g (both presentations will be used in stage 1 of IRC);
- Metformin XR is effective on both fasting and postprandial blood glucose levels.

Secondary hypothesis:

- Metformin XR is well tolerated in moderate (stage 3B) IRC, without development of hyperlactatemia.

7 STUDY OBJECTIVES

Primary Objective

Evaluate the efficacy of metformin XR on 24-hour blood glucose

Secondary Objective

- Evaluate the metabolic tolerance of metformin XR in CKD (as assessed by lactatemia).
- Compare the intake of 2 tablets of metformin XR 500 mg with that of 1 tablet 1 g (in stage 1 of CKD) compared to their effect on blood sugar.
- Evaluate the efficacy of metformin XR on fasting glucose and postprandial blood glucose levels.

8 INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN

The study is a clinical trial of a drug

- prospective
- non-randomized;
- in phase 2 (partial contraindication with renal insufficiency in stage 3B of CKD
- comparative: with intra-group comparisons (the parameters of interest are compared according to the different doses of metformin) and intergroups (for the same dose of metformin)
- without insulin
- monocentric.

8.2 SELECTION OF STUDY POPULATION

8.2.1 INCLUSION CRITERIA

- Diabetic patients treated with or treated with metformin, alone or in combination with other antidiabetics, and having a CKD stage 1 or 3B of chronic renal insufficiency (the pharmacological treatment being reserved for the failure of the well-conducted nutritional treatment, Type 2 diabetes must therefore have a minimum of tenure to justify treatment with metformin. In practice, we opt for a period of at least 6 months);
- Patients aged 18 to 80 years;

- Patients with a renal and hepatic function test within the last 3 months;
- Patients with stable renal function, based on the criterion of no more than 30% fluctuation in creatinine clearance (as measured by the MDRD formula) within a period of at least 3 months, Inclusion is therefore necessary).
- Patients treated with ACE inhibitors or angiotensin II receptor antagonists (ARA2) should have stable dosages in the study.

8.2.2 EXCLUSION CRITERIA

- Absence of previous creatinine reference;
- Fluctuation of more than 30% of renal creatinine clearance function (measured by MDRD formula) during the last three months;
- Severe hepatic insufficiency (stage Child> A);
- No reference to liver function for stage 3;
- Patients who require X-ray contrast media injection;
- Pregnant or breastfeeding women;
- Hypersensitivity to metformin or to any of the excipients;
- Diabetic Keto-acidosis or diabetic pre-coma;
- Any acute general condition liable to impair renal function (cardiac or respiratory insufficiency, myocardial infarction, shock, etc.);
- Any general acute condition accompanied by a lactate> 2.5 mmol / l;
- Acute alcohol intoxication or alcoholism (drinking more than 3 drinks per day).
- Participation in another clinical trial
- Persons deprived of their liberty, hospitalized or admitted for purposes other than research.
- Adult person under guardianship or not in a condition to express its consent.

8.3 TREATMENTS

8.3.1 TREATMENTS ADMINISTERED

Long-acting metformin (XR or SR) is currently not available in France.
Like in metformin IR (immediate release: Glucophage®) the active treatment is the hydrochloride salt of metformin. The available formulations of the extended-release metformin are in the form of 500, 750, and 1000 mg tablets. The treatment is administered orally. Some countries already have a marketing authorization for this treatment, ie in Croatia, Hungary, Latvia, Poland, Czech Republic, Romania, United Kingdom, Slovakia (source: European Medicines Agency, Dec. 3, 2015).
In the absence of chronic renal insufficiency, the usual dosage of metformin XR is between 1500 mg and 2000 mg per day in a single dose. This dose should be reduced in chronic renal insufficiency, in line with the approved UK label: 2000mg/day in CKD stage 2 and 3A, 1000mg in CKD stage 3B
The contraindications of metformin XR are the same as for metformin IR, in the forefront of which is chronic renal insufficiency.
The study will involve 12 patients with CKD IRC stage 3B (creatinine clearance from 44 to 30 ml / min / 1.73 m^2).

8.3.2 DESCRIPTION OF INVESTIGATIONAL PRODUCTS

1. TREATMENT ON SUTDY

Long-acting metformin (XR or SR) is currently not available in France.
Like in metformin IR (immediate release: Glucophage®) the active treatment is the hydrochloride salt of metformin. The available formulations of the extended-release metformin are in the form of 500, 750, and 1000 mg tablets. The treatment is administered orally. Some countries already have a marketing authorization for this treatment, ie in Croatia, Hungary, Latvia, Poland, Czech Republic, Romania, United Kingdom, Slovakia (source: European Medicines Agency, Dec. 3, 2015).
In the absence of chronic renal insufficiency, the usual dosage of metformin XR is between 1500 mg and 2000 mg per day in a single dose. This dose should be reduced in chronic renal insufficiency, in line with the approved UK label: 2000mg/day in CKD stage 2 and 3A, 1000mg in CKD stage 3BThe contraindications of metformin XR are the same as for metformin IR, in the forefront of which is chronic renal insufficiency.

The study will involve 12 patients with CKD stage 3B (44-30 ml/min/1,73 m²).

2. COMAPRATIVE TREATMENT

There is no comparison. Metformin XR in particular is not compared to the conventional formulation of metformin; It is simply the doses of metformin XR that are compared with each other.

3. PRODUCT DESCRIPTION

i. PRODUCT SUPPLY

The product under study is supplied by Merck KGaA in the form of the specialty Glucophage SR® marketed in the United Kingdom.
The product is then delivered by the pharmacy for internal use (PUI) of the CHU Amiens-Picardie.

ii. PRODUCT PACKAGING

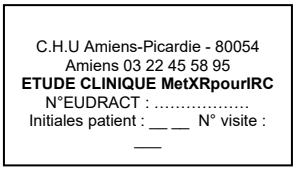
The product under study is conditioned by the Merck KGaA
Three different dosages are available:

- Box of 28 tablets of Metformin XR 500 mg
- Box of 28 tablets of Metformin XR 750 mg
- Boxes of 28 tablets of Metformin XR 1000 mg.

The primary packaging of metformin is a blister of 14 tablets: blister pack made of PVC or PVC / PVDC and aluminum foil.
The secondary packaging is a box with a minimum size of 69 x 21.5 x 126 mm containing 2 blister packs of 14 tablets.

iii. PRODUCT LABELLING

The product specific labeling of the products under study is carried out by the PUI of Amiens-Picardie University Hospital for the purpose of affixing the prescribed indications for use in the context of biomedical research.
Primary packaging already contains information on the Glucophage SR®: Trade name, INN, dosage, batch and expiration date.
Additional labeling is affixed to this primary packaging so as not to obscure the information already present. The glued label is as follows:



Secondary packaging already contains information on Glucophage SR®: Trade name, INN, dosage, composition, batch and expiration date.
Additional labeling is affixed to this primary packaging so as not to obscure the information already present, in particular the name of the Glucophage SR®, the INN, the dosage, the batch number and the expiry date (information already on the Primary packaging).

The adhesive labels are the following according to the dosage of the drug:

CHU Amiens- Picardie - 80054 Amiens
03.22.45 58 95
ETUDE CLINIQUE MetXRpourIRC Pr Lalau
EudraCT :……..
Centre n° : **01**

Numéro du patient : └ ┘ └ ┘
Initiales du patient : └ └┘
Médecin investigateur : ……..

Metformine XR 500 mg
Boite de 28 comprimés **Per os**
Respecter les doses prescrites

A conserver à température ambiante.
MEDICAMENT POUR RECHERCHE BIOMEDICALE UNIQUEMENT
NE PAS LAISSER A LA PORTEE DES ENFANTS

CHU Amiens- Picardie - 80054 Amiens
03.22.45.58.95
ETUDE CLINIQUE MetXRpourIRC Pr Lalau
EudraCT :……..
Centre n° : **01**

Numéro du patient : └ ┘ └ ┘
Initiales du patient : └ └┘
Médecin investigateur : ……..

Metformine XR 750 mg
Boite de 28 comprimés **Per os**
Respecter les doses prescrites

A conserver à température ambiante.
MEDICAMENT POUR RECHERCHE BIOMEDICALE UNIQUEMENT
NE PAS LAISSER A LA PORTEE DES ENFANTS

CHU Amiens- Picardie - 80054 Amiens
03.22.45.58.95
ETUDE CLINIQUE MetXRpourIRC Pr Lalau
EudraCT :……..
Centre n° : **01**

Numéro du patient : └ ┘ └ ┘
Initiales du patient : └ └┘
Médecin investigateur : ……..

Metformine XR 1000 mg
Boite de 28 comprimés **Per os**
Respecter les doses prescrites

A conserver à température ambiante.
MEDICAMENT POUR RECHERCHE BIOMEDICALE UNIQUEMENT
NE PAS LAISSER A LA PORTEE DES ENFANTS

Labeling of primary and secondary packaging is provided by the PUI of the University Hospital of Amiens.

iv. PRODUCT STORAGE

Pending delivery, products are stored at room temperature in the clinical trial area of the PUI with secure access in their secondary packaging.

v. PRODUCT DISPENSATION

Treatments are provided by the PUI of the CHU Amiens-Picardie in accordance with the internal procedures in force in the establishment.
They are given to the patient or to the nursing service on presentation of a typical prescription (Schedule 1), during scheduled visits for 14 days of treatment: in S0, S2 and S4 for all patients included (CKD stages 1 and 3B).

The patient's initials, its inclusion number and the name of the investigating physician are completed on the secondary packaging label by the pharmacist (or any other person under delegation) at the time of issue. A copy of the prescription is given to the patient.
Patients will report their treatment at the next visit. The used and unused blisters of Metformin XR are returned to the PUI to ensure the accounting of therapeutic units.

vi. STOCK

Metformin XR is stored at room temperature in a room with secure access dedicated to experimental PUI treatments.
The units returned by the patients are kept in the quarantine area dedicated to the clinical trials of the PUI pending their destruction.

vii. RETURN AND DESTRUCTION OF UNUSED PRODUCTS

Since medicines are prescribed in a clinical trial, treatment accounting is performed by the PUI Clinical Trials Unit at Amiens - Picardie University Hospital.

Thus, after returning used and unused units to the PUI, the pharmacist responsible for clinical trials (or any other person under delegation) performs an inventory of the products used and not used according to the internal procedures.
The products are destroyed after agreement of the sponsor, with production of a certificate of destruction according to the internal procedure.

8.4 DATA QUALITY ASSURANCE

I. Information on Data collection

All the information required by the protocol must be recorded as it is obtained in the electronic observation book and an explanation must be given for each missing data. Any access to the data of the study and their possible modification will be plotted using the Clinsight® software.

II. Research Monitoring

The research will be monitored by a clinical research technician. He will be responsible for coordinating:

- logistics and monitoring of research,
- reporting on its progress,
- verification of the updating of the observation book (request for additional information, corrections, ...),
- sending of excerpts,
- the transmission of SAEs to the sponsor.

He will work in accordance with standard operating procedures, in collaboration with the clinical research officer delegated by the proponent.

III. Quality Control

A clinical researcher mandated by the sponsor visits the research center on a regular basis, when the research is set up, once or several times during the course of research, according to the rhythm of the inclusions and at the end of the research. During these visits, the following elements will be reviewed:

- Informed consents,
- Following of the research protocol and the procedures defined therein,
- Quality of the data collected in the observation book: accuracy, missing data, consistency of data with source documents (medical records, appointment books, originals of laboratory results, etc.),
- Management of potential conditions.

Any visit will be the documented in a monitoring report in writing.

IV. Data management on study competion

The data will be captured in an electronic observation booklet on the Clinsight® software. The protocol data will be simply entered in the e-CRF directly by the lead investigator or the authorized persons, referenced on the delegation of tasks list.
The parameterized consistency tests will verify the quality of the data. Correction requests will be sent to the investigator in the event that inconsistencies are detected.

The data are validated according to the data management plan defined jointly by the principal investigator and the Center for Methodology and Data Management (methodologist, data manager and statistician). The software used is: Clinsight® and SAS®.

The process of freezing / thawing the data is carried out in accordance with the procedure set up in the Center for Methodology and Data Management.

V. Audit and inspection

An audit can be carried out at any time by persons mandated by the sponsor and independent of the researchers. Its objective is to ensure the quality of the research, the validity of its results and the respect of the law and the regulations in force.

The investigators agree to comply with the requirements of the Proponent and the Competent Authority with respect to an audit or research inspection.

The audit can be applied at all stages of research, from the development of the protocol to the publication of the results and the classification of the data used or produced in the research.

8.5 STATISTICAL METHODS PLANNED IN THE PROTOCOL & DETERMINATION OF SAMPLE SIZE

8.5.1 DETERMINATION OF SAMPLE SIZE

This is a Phase II study of a limited number of patients that aims to move to a larger study in case of encouraging results. A total of 24 patients is planned with the following distribution:

- Group 1 (12 patients): GFR>90 ml/min (Normal renal function or mild renal insufficiency, stage 1 of IRC)
- Group 2 (12 patients): GFR 44-30 ml/min (moderate renal insufficiency, stage 3b of IRC)

8.6 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Due to the difficulty in recruiting CKD stage 1 patient (with the need of additional 24-hours hospitalization periods), it was decided to continue the study with the sole CKD stage 3B group. Therefore, an assessment of two of the primary objectives of the study, namely whether the once daily dosing of metformin extended release is effective on blood glucose control and whether there is an equivalence of metformin XR effect on blood glucose of 500mg (2 tablets) versus 1000 mg (one tablet) (in CKD 1) are not possible.

9 RESULTS

9.1 DATA SETS ANALYSED

The 12 CKD 3B patients included completed the study.

9.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The patients' baseline characteristics are as follows (mean±SD):

Age, years	65.6 (3.9)
Gender, M/F	6 / 6
BMI, kg/m^2	32.3 (5.3)
Blood glucose, mmol/l	8.39 (2.96)

A1C, %	7.63 (1.09)
eGFR, ml/min/1.73 m^2	32.8 (7.0)
No. of antidiabetic classes:	
0	0
1	0
2	1
3	7
4	3
5	1

Metformin (IR) treatment prior to inclusion

Salt formulation	Daily dose, mg	Base Daily dose, mg	No. of patients
Hydrochloride	500	390	3
	1,000	780	3
	1,700	1326	1
	2,000	1560	1
	3,000	2340	1
Embonate	700	280	1
	2,100	840	2

The average daily metformin dose was 891mg metformin base (equaling 1144 mg metformin hydrochloride) . Of 12 included patients, only three (3) were on the lowest of the test doses, and 5 were exceeding the maximum recommended daily dose of metformin in CKD stage 3B, namely 780mg base.

Details about the eGFR (mL/min/1.73 m^2) course throughout the study.

Patient	Pre-inclusion [range]	Inclusion	Visit 1	Visit 2	Visit 3	Final decision for maintenance into 3B stage group
1	30.4-44.5	38	31	35	37	Normal
2	26.6-31	27	28	27	24	Low
3	37.8-45	42	43	41	42	Normal
4	28-40	30	40	38	31	Normal
5	43-45	47	49	48	53	High
6	25.9-29.4	27	28	30	28	Low
7	33-37	30	36	40	37	Normal
8	30-32	26	32	33	31	Normal
9	39-45	37	38	44	36	Normal
10	32.7-40.6	26	40	35	35	Normal
11	33-36	28	27	26	27	Low
12	35.9-38.9	36	35	41	40	Normal

8 of the patients (subjects 1,3,4,7,8,9,10,12) were stable in CKD stage 3 throughout the cluster. One patient (subject 5) was in CKD stage 3A, and three patients were, at least in part, in CKD stage 4. They form the groups normal, low and high in the table above.

9.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Glucophage® tablets were given by a nurse at the time of the PK study.
Metformin XR tablets taken were then counted by a nurse at each visit, before the dispensation of a new metformin XR dosage.

9.4 STUDY DURATION

This was a three 2-week sequence clinical study, i.e. for a total of 6 weeks.

9.5 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENTS DATA

9.5.1 ANALYSIS OF EFFICACY

The efficacy of metformin XR was assessed at the end of each study phase by measuring HA1c level and, more accurately, by collecting data about continuous glucose monitoring (CGM).

HBA1c levels and CGM metrics are shown as follows:

	Inclusion	Visit 1 (500 mg)	Visit 2 (750 mg)	Visit 3 (1,000 mg)	Comparison between the dosages (p-value)
Measured A1c, %	7.63±1.09	8.09±1.11	8.56±1.58	8.78±1.98	0.5847
CGM metrics*:					
Mean glycaemia, mmol/l	-	10.9±3.5	12.1±6.2	11.1±5.0	0.8225
Time in range, %	-	42.4±24.9	49.7±30.9	44.6±23.4	0.7896
Time above range, %	-	54.7±27.0	48.1±32.1	51.8±24.3	0.8464
Time below range, %	-	2.9±4.8	2.2±3.1	5.1±10.1	0.5482
Glycemic variability, % CV	-	28.8±7.8	29.5±11.8	27.7±9.5	0.9032
Estimated A1C, %	-	8.81±2.39	9.14±4.03	8.74±3.16	0.9499
Estimated A1c, mmol/l	-	72.8±26.2	76.8±44.2	71.8±34.6	0.9366

*: The LibreView software was not used during the first treatment phase of the study of the study (with metformin XR 500 mg) for the first 3 patients included who entered into the study with their own sensor; this disposal was used for the subsequent phases in those patients and for all phases in others.

9.5.2 STATISTICAL/ANALYTICAL ISSUES

9.5.2.1 HANDLING OF DROPOUTS OR MISSING DATA

Antidiabetic drugs exposure at baseline and modifications throughout the study.

P	Number drugs	Baseline			Modifications during the study		
		Metformin dose /day	Metformin base /day	Non-metformin therapy	Phase 1 (500 mg)	Phase 2 (750 mg)	Phase 3 (1000 mg)
1	3	500 mg HCl	390mg	Insulin: aspart + detemir	–	–	↓ detemir: 24 → 28 U
2	3	500mg HCl	390mg	Liraglutide Insulin: glargine	–	–	–
3	3	1700mg HCl	1326mg	Repaglinide Insulin: isophane	↑ isophane: 20 → 28 U	↑ isophane: 28 → 38 U	–
4	4	1000mg HCl	780mg	Vildagliptine Insulin: lispro, isophane	–	–	–
5	2	3 tablets EMB	840mg	Insulin: degludec	–	–	–
6	3-4	500mg HCl	390mg	Gliclazide Long-acting exenatide +/- insulin: aspart	–	–	–
7	3	3000mg HCl	2340mg	Gliclazide Saxagliptin	–	–	–
8	4	2000mg HCl	1560mg	Gliclazide Insulin: aspart/degludec	–	–	–
9	4	1000mg HCl	780mg	Repaglinide Insulin: aspart/protamin	–	–	–
10	4	1000mg HCl	780mg	Liraglutide Repaglinide Insulin: isophane	↑ insulin (marked but intermittent)	–	–
11	3	1 tablet EMB	280mg	Liraglutide Insulin: degludec	–	–	–
12	5	3 tablets EMB	840mg	Gliclazide Liraglutide Insulin: lispro/protamine	–	–	–

11 of 12 patients were on Insulin. Throughout the study, the insulin dose was changed in three patients (1, 3, 10), in line with protocol section “It will be at the discretion of the investigator to initiate complementary antidiabetic treatment other than that of biguanides and / or to strengthen an existing adjunct therapy (sulphonamide, alpha-glucosidase inhibitors, gliptins, GLP- 1, and insulin), any routine procedure in diabetes practice”. In the one patient not on insulin, but on the highest pre-study metformin dose (3000mg HCl, patient 7), marked hyperglycemia occurred.

Glycemic control was planned to be assessed in the study group with CKD stage 1, which was not enrolled. It is to be expected that glycemic control is decreased when metformin daily dose is lowered for the course of the study. Patient 7 was excluded in the glycemic result analysis for CKD stage 3B, and the data below include 11 patients with an average daily metformin dose of 760mg metformin base (equaling 760mg metformin base or 974mg metformin hydrochloride).

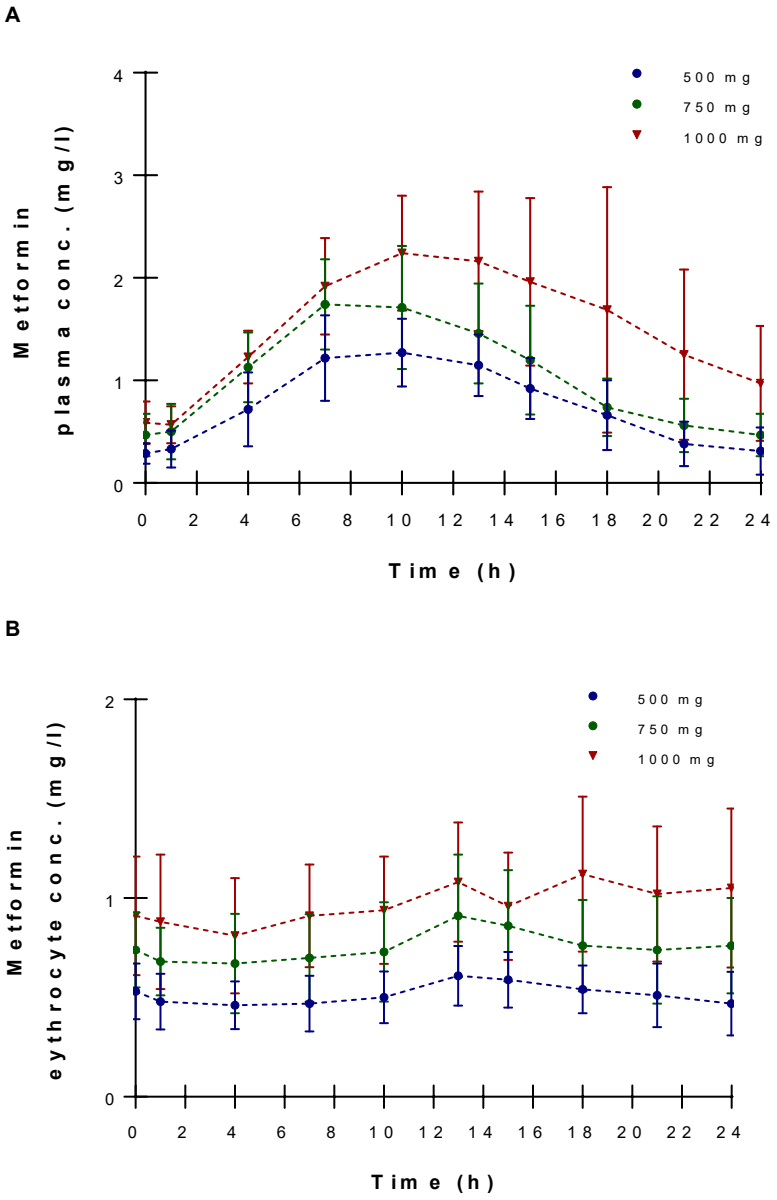
	Inclusion	**Visit 1 (500 mg)**	**Visit 2 (750 mg)**	**Visit 3 (1,000 mg)**	**Comparison between the dosages (p-value)**
Measured A1c, %	7.63±1.15	7.95±1.05	8.17±0.88	8.25±0.87	0.7413
CGM metrics:					
Mean glycaemia, mmol/l	-	10.1±2.2	10.3±3.2	9.7±1.6	0.8406
Time in range, %	-	45.7±23.2	55.9±26.4	48.7±19.6	0.5771
Time above range, %	-	51.1±25.2	41.6±27.3	47.5±19.9	0.6561
Time below range, %	-	3.1±4.9	2.5±3.2	5.6±10.5	0.5461
Glycemic variability, %	-	28.7±8.2	32.4±8.5	29.5±7.5	0.5349
Estimated A1C, %	-	8.32±1.77	7.99±2.20	7.89±1.19	0.8379
Estimated A1c, mmol/l	-	67.4±19.3	64.1±24.2	62.5±13.3	0.8315

It is evident that measured HbA1c (mid-term glycemic marker) deteriorates with the reduced dose and continues to do so when metformin is titrated back up to average pre-study dose, whereas estimated HbA1c improves with increased dose (measured and estimated A1c values are not necessarily equivalent since measured values provide a direct information (about glycation) on 3 months while estimated values provide an indirect information about each 2-week study phase.

9.5.3 TABULATION OF INDIVIDUAL RESPONSE DATA

The 24-hours kinetics of metformin XR in plasma and in erythrocytes appear in **Figure 1**. In this analysis, all 12 subjects are included.

Figure 1. Metformin concentration over time in plasma (A) and in erythrocytes (B) after the oral administration of a dose of 500 mg, 750 mg, or 1000 mg of metformin in steady-state (mean ± SD)

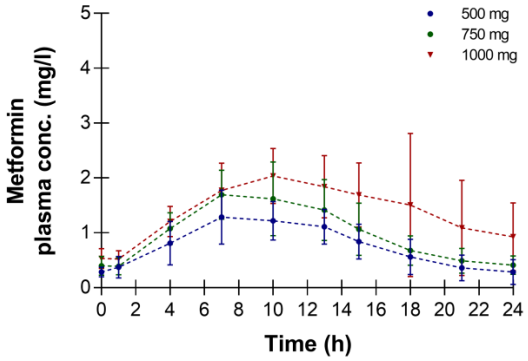


It is evident that metformin plasma concentration is higher with higher daily doses of metformin. The formulation leads to increased plasma levels for 8-11 hours post administration. Steady state metformin erythrocyte concentrations are not fluctuating over 24 hours, but still higher with increased doses.

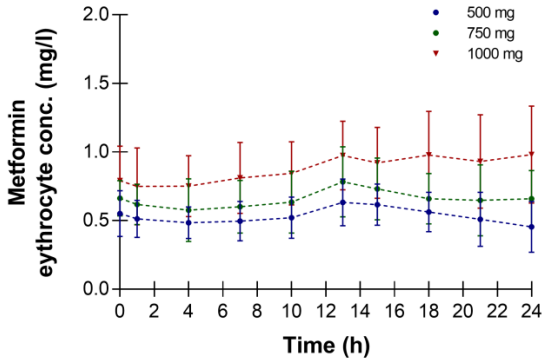
The patients have further been grouped in line with section 9.2.

Stable CKD 3B
(patients 1, 3, 4, 7, 8, 9, 10 and 12)

Plasma

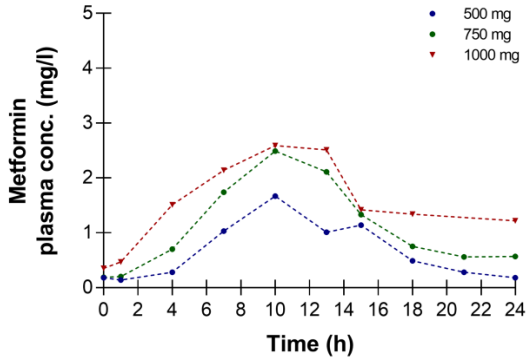


Erythrocytes

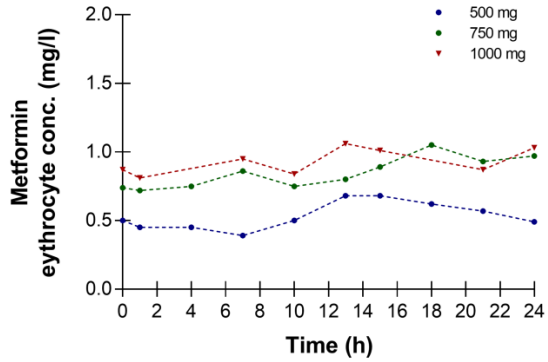


CKD 3B-3A
(patient 5)

Plasma

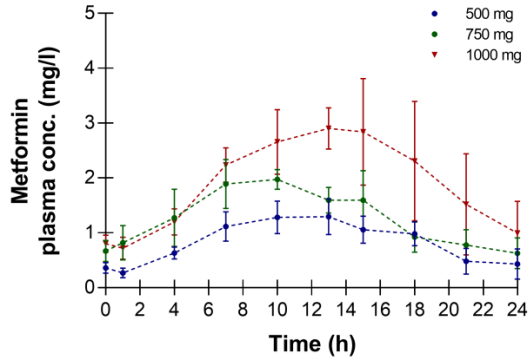


Erythrocytes

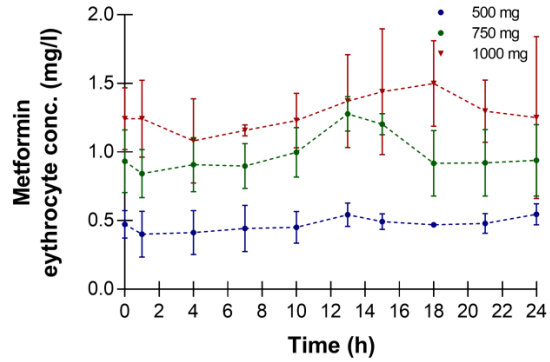


CKD 3AB-4
(patients 2, 6 and 11)

Plasma



Erythrocytes



There is no difference between the patients fully in line with CKD stage 3B and the patient in CKD stage 3A-3B. In contrast, the patients even only in part in CKD stage 4 show larger metformin plasma concentrations at the highest dose of 1000mg/day. Regarding metformin plasma concentration, already the daily dose of 750mg led to higher “deep compound load” with metformin.

Overall PK parameters for metformin XR in plasma and erythrocytes [mean±SD (range)].

Parameters	Compartment	Visit 1 500 mg	Visit 2 750 mg	Visit 3 1,000 mg	ANOVA p-value
C_{max}, mg/l	Plasma	1.4 ± 0.4	1.9 ± 0.5	2.6 ± 0.9	0.0003
		(0.8 – 2.3)	(0.8 – 2.5)	(0.9 – 4.5)	
	Erythrocyte	0.7 ± 0.1	1 ± 0.2	1.2 ± 0.3	<0.0001
		(0.4 – 0.8)	(0.6 – 1.4)	(0.5 – 1.9)	
T_{max}, h	Plasma	9.5 ± 2.5	8.2 ± 2.8	10.8 ± 3.1	0.0618
		(7 – 13)	(4 – 15)	(7 – 18)	
	Erythrocyte	13.1 ± 2.8	14 ± 1.6	16 ± 4.5	0.3096
		(7 – 18)	(13 – 18)	(10 – 24)	
$T_{1/2}$*, h	Plasma	5.3 ± 2.3	6.5 ± 1.4	7.1 ± 3.2	0.1788
		(2.1 – 9.6)	(3.9 – 10)	(3.7 – 14.1)	
	Erythrocyte	41.1 ± 37.5	56.5 ± 42.9	66.5 ± 56.7	0.3504
		(3.8 – 131.1)	(9.1 – 178.9)	(5.1 – 155.3)	
AUC_{24}, h·mg/l	Plasma	19.2 ± 4.6	26.2 ± 7.2	38.1 ± 11.2	<0.0001
		(11.1 – 28.9)	(12.8 – 36.4)	(16.3 – 55.1)	
	Erythrocyte	12.8 ± 3.4	18.9 ± 5.3	24.1 ± 7.8	0.0002
		(7.1 – 18)	(7.7 – 25.9)	(9.2 – 37)	
$AUC_{0-\infty}$*, h·mg/l	Plasma	22.2 ± 7.1	31.8 ± 11.6	49.1 ± 16.2	<0.0001
		(11.7 – 34.1)	(13.6 – 57.5)	(17.7 – 65.6)	
	Erythrocyte	46 ± 34.5	81.9 ± 68.2	131.5 ± 113	0.0563
		(10.9 – 127)	(26.6 – 263.6)	(18 – 350.3)	
C_{24h}, mg/l	Plasma	0.3 ± 0.2	0.5 ± 0.2	1 ± 0.6	0.0061
		(0.1 – 0.7)	(0.2 – 0.9)	(0.2 – 1.9)	

	Erythrocyte	0.5 ± 0.2	0.8 ± 0.2	1.1 ± 0.4	0.0002
		(0.2 – 0.7)	(0.3 – 1.1)	(0.3 – 1.8)	
C_{avss}, mg/l	Plasma	0.8 ± 0.2	1.1 ± 0.3	1.6 ± 0.5	<0.0001
		(0.5 – 1.2)	(0.5 – 1.5)	(0.7 – 2.3)	
	Erythrocyte	0.5 ± 0.1	0.8 ± 0.2	1 ± 0.3	0.0002
		(0.3 – 0.7)	(0.3 – 1)	(0.4 – 1.5)	

Abbreviations: AUC, area under the concentration versus time curve; Cavss, average concentration within 24h dose interval in steady state; Cmax, maximal concentration; C24h, concentration 24h after dose intake; Tmax, time to maximal concentration after dose intake; $T_{1/2}$, half-life time.
* $T_{1/2}$ and $AUC_{0-\tau}$ could not have been determined in 4 cases due the lack of concentration decay within the 24 h-interval.

The pK parameters have further been stratified and are presented below for the CKD stage 3B and the CKD 3B-4 group (see below). The data clearly highlights the difference in the patients' parameters for $c_{max\ plasma}$ 2.4 ± 1 vs 3.2 ± 0.6 mg/l and AUC_{24} (34.3 ± 10.6 47.4 ± 10.4 (h·mg/l) at 1000mg/day. Already for 750mg/day, $c_{max\ erythrocyte}$, was significantly higher in the CKD 3B-4 group with 1.3 ± 0.1 mg/l versus 0.9 ± 0.2 mg/l in the CKD stage 3B group.

PK parameters for patients with stable CKD 3B (patients 1, 3, 4, 7, 8, 9, 10 and 12) [mean±SD (range)].

Parameters	**Compartment**	**Visit 1 500 mg** N=8	**Visit 2 750 mg** N=8	**Visit 3 1,000 mg** N=8	**Comparison of the dose regimen (ANOVA p-value)**
C_{max}, mg/l	Plasma	1.4 ± 0.4	1.8 ± 0.5	2.4 ± 1	0.0272
		(0.8 – 2.3)	(0.8 – 2.5)	(0.9 – 4.5)	
	Erythrocyte	0.7 ± 0.2	0.9 ± 0.2	1.1 ± 0.3	0.0083
		(0.4 – 0.8)	(0.6 – 1.4)	(0.5 – 1.9)	
T_{max}, h	Plasma	9.25 ± 2.7	7 ± 1.6	10.6 ± 3.5	0.0446
		(7 – 13)	(4 – 10)	(7 – 18)	
	Erythrocyte	13.4 ± 0.9	13.6 ± 1	16 ± 5.4	0.3252
		(13 – 15)	(13 – 15)	(10 – 24)	
$T_{1/2}$*, h	Plasma	5.1 ± 1.8	6.6 ± 1.6	7.1 ± 2.6	0.1415
		(3.5 – 9.6)	(4.1 – 10.7)	(3.7 – 14.1)	

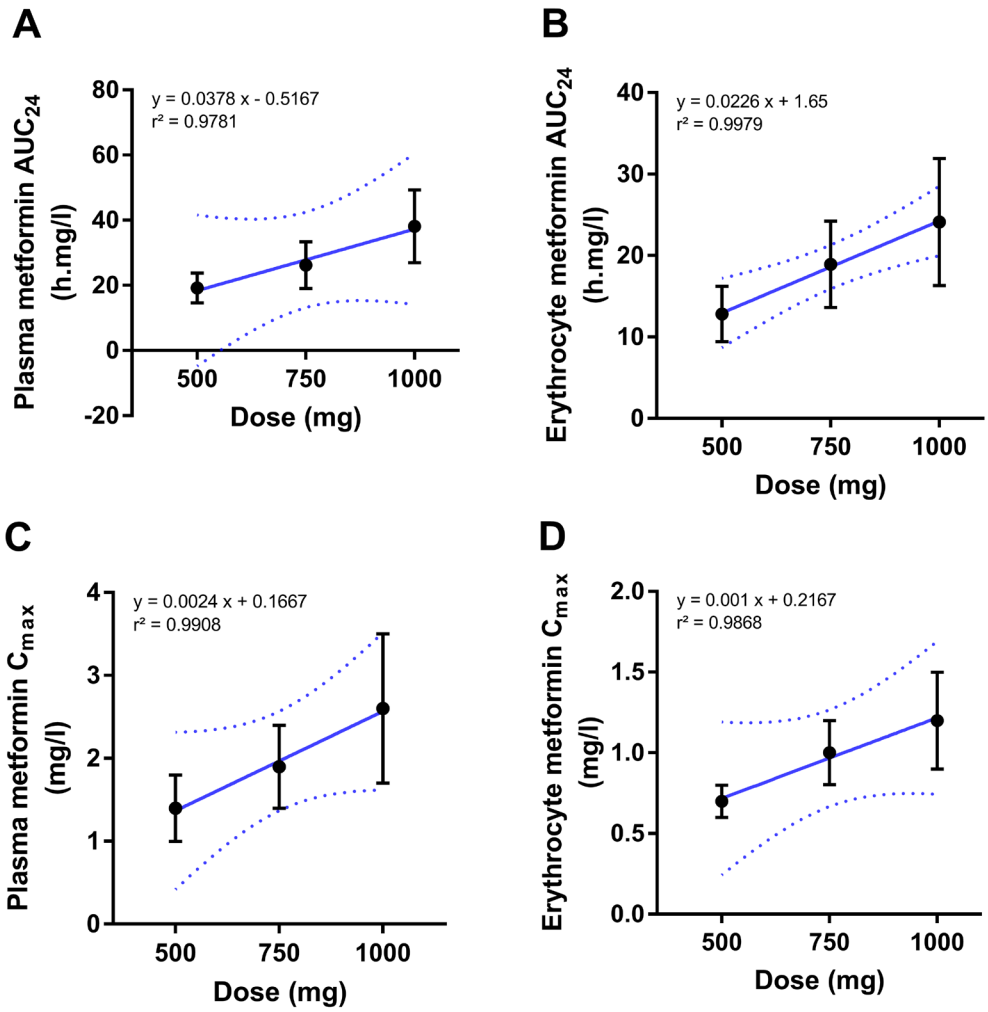
	Erythrocyte	33.1 ± 26.4	62.3 ± 50.2	56.4 ± 55.7	0.4051
		(4.8 – 82.5)	(24.4 – 178.9)	(20.4 – 152.1)	
AUC_{24}, h·mg/l	Plasma	18.9 ± 5.5	23.9 ± 7.7	34.3 ± 10.6	0.0038
		(11.1 – 28.9)	(12.8 – 36.4)	(16.3 – 53.1)	
	Erythrocyte	13.6 ± 3.6	17 ± 5.1	22.1 ± 7.8	0.0253
		(7.1 – 18)	(7.7 – 22.4)	(9.2 – 35.4)	
$AUC_{0-\infty}$*, h·mg/l	Plasma	1.4 ± 0.4	1.8 ± 0.5	2.4 ± 1	0.0272
		(0.8 – 2.3)	(0.8 – 2.5)	(0.9 – 4.5)	
	Erythrocyte	0.7 ± 0.2	0.9 ± 0.2	1.1 ± 0.3	0.0083
		(0.4 – 0.8)	(0.6 – 1.4)	(0.5 – 1.9)	
C_{24h}, mg/l	Plasma	0.3 ± 0.2	0.4 ± 0.2	0.7 ± 0.2	0.0038
		(0.1 – 0.7)	(0.2 – 0.7)	(0.4 – 1.9)	
	Erythrocyte	0.5 ± 0.2	0.7 ± 0.2	1 ± 0.4	0.0021
		(0.4 – 0.8)	(0.6 – 1.1)	(0.5 – 1.4)	
C_{avss}, mg/l	Plasma	0.8 ± 0.2	1 ± 0.3	1.4 ± 0.4	0.0038
		(0.5 – 1.2)	(0.5 – 1.5)	(0.7 – 2.2)	
	Erythrocyte	0.6 ± 0.2	0.7 ± 0.2	0.9 ± 0.3	0.0253
		(0.3 – 0.7)	(0.3 – 0.9)	(0.4 – 1.5)	

PK parameters for patients with CKD 3B-4 (patient 2, 6 and 11) [mean±SD (range)].

Parameters	**Compartment**	**Visit 1 500 mg** N=3	**Visit 2 750 mg** N=3	**Visit 3 1,000 mg** N=3	**Comparison of the dose regimen (ANOVA p-value)**
C_{max}, mg/l	Plasma	1.4 ± 0.2	2.2 ± 0.3	3.2 ± 0.6	0.0057
		(1.3 – 1.6)	(1.9 – 2.4)	(2.5 – 3.8)	
	Erythrocyte	0.6 ± 0.1	1.3 ± 0.1	1.5 ± 0.3	0.0016
		(0.5 – 0.6)	(1.2 – 1.4)	(1.3 – 1.9)	
T_{max}, h	Plasma	10 ± 3	10.7 ± 4	11.7 ± 2.9	0.8332
		(3 – 13)	(7 – 15)	(10 – 15)	
	Erythrocyte	12.7 ± 5.5	13.7 ± 1.2	17 ± 1.7	0.3311
		(7 – 18)	(13 – 15)	(15 – 18)	

$T_{1/2}$*, h	Plasma	6.3 ± 3.8	6.6 ± 1.4	4.9 ± 1.2	0.6733
		(2.1 – 9.6)	(5.1 – 7.9)	(3.7 – 6)	
	Erythrocyte	84.3 ± 66.3	42.3 ± 29.6	72.6 ± 76.2	0.7240
		(37.4 – 131.1)	(9.1 – 65.9)	(5.1 – 155.3)	
AUC_{24}, h·mg/l	Plasma	20.7 ± 2.6	31.4 ± 3.9	47.4 ± 10.4	0.0073
		(17.9 – 23)	(27 – 34.4)	(35.6 – 55.1)	
	Erythrocyte	10.7 ± 2.6	23.7 ± 3.6	30.6 ± 6.2	0.0043
		(8.4 – 13.5)	(19.5 – 25.9)	(24.6 - 37)	
$AUC_{0-\infty}$*, h·mg/l	Plasma	25.6 ± 6.1	41.8 ± 14.1	54.9 ± 15.3	0.0762
		(18.2 – 30.2)	(29.9 – 57.5)	(37.4 – 65.4)	
	Erythrocyte	81.9 ± 63.8	88.2 ± 53.3	186.5 ± 160.8	0.5080
		(36.8 - 127)	(27.9 – 128.7)	(29 – 350.3)	
C_{24h}, mg/l	Plasma	0.4 ± 0.3	0.6 ± 0.3	0.9 ± 0.3	0.1487
		(0.1 – 0.6)	(0.4 – 0.9)	(0.6 – 1.1)	
	Erythrocyte	0.5 ± 0.1	0.9 ± 0.3	1.3 ± 0.6	0.1236
		(0.4 – 0.6)	(0.6 – 1.1)	(0.6 – 1.7)	
C_{avss}, mg/l	Plasma	0.9 ± 0.1	1.3 ± 0.2	2 ± 0.4	0.0073
		(0.7 – 1)	(1.1 – 1.4)	(1.5 – 2.3)	
	Erythrocyte	0.4 ± 0.1	1 ± 0.2	1.3 ± 0.3	0.0043
		(0.3 – 0.6)	(0.8 – 1.1)	(1 – 1.5)	

Figure 2. Linear regression profile with 95% confidence interval of metformin AUC_{24} versus dose (A and B) and C_{max} versus dose (C and D), in plasma (A and C) and erythrocytes (B and D), after the oral administration of a dose of 500 mg, 750 mg, or 1000 mg of metformin XR in steady-state.



Inter-phase (phase 2 and phase 3 *vs*. phase 1) comparisons of the dose-proportionality for AUC_{24} and C_{max}.

Parameters	Compartment	750 mg vs. 500 mg			1000 mg vs. 500 mg		
		GMR	90%CI	Proportionality	GMR	90%CI	Proportionality
AUC_{24}	Plasma	0.97	[0.94-1]	yes	0.99	[0.94-1.04]	yes
	Erythrocyte	0.99	[0.94-1,04]	yes	0.98	[0.93-1.03]	yes

	Plasma	0.98	[0.96-1]	yes	0.98	[0.95-1.01]	yes
C_{max}							
	Erythrocyte	1	[0.98-1.02]	yes	0.98	[0.96-1]	yes

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; GMR, geometric mean ratio.

9.5.4 DRUG DOSE AND RELATIONSHIP TO RESPONSE

A correlative study has been performed to look for the relationship between the main parameters of pharmacokinetics and pharmacodynamics. Data are from all patients and all therapeutic phases, whilst controlling for the subject effect (Pearson's correlation coefficient, *p*-value):

A. Plasma

	Mean glycaemia	**Glycaemic variability**	**HbA1c (measured)**
C_{max}	0.274, NS	-0.359, 0.047	0.292, NS
C_{24h}	-0.131, NS	-0.023, NS	-0.105, NS
AUC_{24}	0.114, NS	-0.236, NS	0.129, NS

B. Erythrocytes

	Mean blood glucose	**Glycaemic variability**	**HbA1c (measured)**
C_{max}	-0.058, NS	-0.155, NS	-0.052, NS
C_{24h}	-0.003, NS	-0.226, NS	0.006, NS
AUC_{24}	0.003, NS	-0.246, NS	0.027, NS

C. Erythrocyte/plasma ratio

	Mean blood glucose	**Glycaemic variability**	**HbA1c (measured)**
C_{max}	-0.463, 0.009	0.288, NS	-0.488, 0.005
C_{24h}	0.200, NS	-0.086, NS	0.150, NS
AUC_{24}	-0.012, NS	-0.230, NS	0.003, NS

The 3 pharmacodynamic parameters were inversely correlated with the C_{max}, and that either with the plasma (glycemic variability) or the erythrocyte/plasma ratio (mean blood glucose and HbA1c). These results suggest that, beyond PK data from plasma and erythrocytes (which are, respectively, classical and less common), the more sophisticated approach using the erythrocyte/plasma ratio may provide more accurate information about the efficacy of the cellular transfer of metformin.

9.5.5 EFFICACY CONCLUSIONS

Overall, the following conclusions could be drawn:

- This is the first study having assessed efficacy, safety, and pharmacokinetics in a steady-state during metformin XR treatment at different doses in subjects with type 2 diabetes (T2D) and CKD (stage 3B). Indeed, metformin XR efficacy has been already studied in T2D patients but not in T2DM patients with renal failure.
- Twelve subjects in CKD stage 3B were studied; all have completed the study.
- The status of CKD stage 3B implies a diabetes of a long duration. This accounts for the fact that all patients but one, were receiving at least 3 antidiabetic drugs, including insulin. This polytherapy always included metformin, and that with a metformin dose higher than that recommended in the CKD3B stage in nearly half the patients (in 5 out of the 12 patients). The average metformin dose before study start was 1144 mg metformin hydrochloride. As the patients started the study with 500mg, then continued with 750mg and finished on 1000mg, the mean glycaemia did not decrease throughout the study despite the increase in the metformin dose. Quite in contrast, the largest tested dose was still below the average pre-study dose. Interestingly, the deterioration was only visible in the measured HbA1c, but not in the estimated HbA1c or glycemia: They were no differences regarding the other CGM metrics, in particular for the time outside the target range.
- After the administration of a metformin in the steady-state, the concentration of the drug increased slowly in the plasma for reaching the C_{max} in 10 h and returned close to baseline value within 24 h. In contrast, erythrocyte concentration remained very stable during this 24 h-time interval. The exposure showed dose-proportionality within the 500-1000 mg dosing range. Noticeably, a rather moderate inter-subject variability of the PK parameters was observed.
- Stratification of the patients by their CKD sub-stage (3B or 3B-4) for the first time demonstrated an increase in metformin plasma level occurred in the 1000mg dose, highlighting the need for monitoring of patients in usual care to be followed up on their CKD progression especially in stage 2B, where the 1000mg dose represents the highest authorized dose. In these patients, even the 750mg dose increased the concentration in the deep compartment erythrocytes.

10 SAFETY EVALUATION

Blood lactate concentrations (mean±SD).

Inclusion	Visit 1 (500 mg)	Visit 2 (750 mg)	Visit 3 (1,000 mg)	Comparison between the dosages (p-value)
1.54±0.5	1.16±0.28	1.10±0.37	1.19±0.40	0.8186

No individual lactate value was noticed > 2.5 mmol/l throughout the study. A fortiori, no true hyperlactatemia (i.e. a value > 5 mmol/l) has occurred during the study.

10.1 ANALYSIS OF ADVERSE EVENTS

The non-serious adverse events were either related to another illness (urinary infection, sinusitis or gastroenteritis) or gastrointestinal disorders well known and well described with metformin. These gastrointestinal disorders are currently observed in patients treated with metformin regardless of the renal function of the patients especially at the onset of the treatment.

The 2 serious adverse events observed during the study were right and left cataract extractions in the same patient. These serious adverse events were related to the presence of cataract prior to the inclusion of the patient and not related to the treatment with metformin XR.

10.2 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

Adverse Events (AEs), safety laboratory data, and any efficacy data necessary to assess the safety of the Pharmaceutical Product.

Non Serious Adverse Events

Patient Number	Sex	Event	Date	Grade	Treatment name	Relationship to Treatment	Comment
01002	female	Diarrhea	09/10/2018	2	METFORMINE XR	Experimental drug	
01002	female	Urinary infection	27/09/2018	2	METFORMINE XR	Other illness	
01004	female	Diarrhea, Frequent bowel movements, Belly ache	09/10/2018	2	METFORMINE XR	Experimental drug	
01009	female	Gastroenteritis (3 Loose bowel and 2 emesis on day 4 / familial context)	22/11/2018	2	METFORMINE XR	Other illness	
01009	female	Sinusitis	08/12/2018	1	METFORMINE XR	Other illness	
01010	female	Gastroenteritis	06/12/2018	2	METFORMINE XR	Other	
01011	male	Diarrhea	14/11/2018	2	METFORMINE XR	Experimental drug	
01011	male	Diarrhea	29/11/2018	2	METFORMINE XR	Experimental drug	

Serious Adverse Events

Patient Number	Sex	Event	Date	Grade	Treatment name	Relationship to Treatment	Comment
01001	male	Right cataract extraction	12/09/2018	3	METFORMINE XR	Other illness	Patient included August 31 2018, treatment with metformin started September 13 2018 (500 mg), last intake September 18 2018. Cataract surgeries performed September 12 and 19 2018. The seriousness criteria was hospitalization. The event is not related to the treatment as cataract was present before the inclusion of the patient. Furthermore, as the surgeries were planned before the inclusion, the events should not have been reported.
01001	male	Left cataract extraction	19/09/2018	3	METFORMINE XR	Other illness	

11 CONCLUSION

Overall, the following conclusions could be drawn:

- This is the first study having assessed efficacy, safety, and pharmacokinetics in a steady-state during metformin XR treatment at different doses in subjects with type 2 diabetes (T2D) and CKD (stage 3B). Indeed, metformin XR efficacy has been already studied in T2D patients but not in T2DM patients with renal failure.
- Twelve subjects in CKD stage 3B were studied; all have completed the study.
- The status of CKD stage 3B implies a diabetes of a long duration. This accounts for the fact that all patients but one, were receiving at least 3 antidiabetic drugs, including insulin. This polytherapy always included metformin, and that with a metformin dose higher than that recommended in the CKD3B stage in nearly half the patients (in 5 out of the 12 patients). The average metformin dose before study start was 1144 mg metformin hydrochloride. As the patients started the study with 500mg, then continued with 750mg and finished on 1000mg, the mean glycaemia did not decrease throughout the study despite the increase in the metformin dose. Quite in contrast, the largest tested dose was still below the average pre-study dose. Interestingly, the deterioration was only visible in the measured HbA1c, but not in the estimated HbA1c or glycemia: They were no differences regarding the other CGM metrics, in particular for the time outside the target range.
- After the administration of a metformin in the steady-state, the concentration of the drug increased slowly in the plasma for reaching the C_{max} in 10 h and returned close to baseline value within 24 h. In contrast, erythrocyte concentration remained very stable during this 24 h-time interval. The exposure showed dose-proportionality within the 500-1000 mg dosing range. Noticeably, a rather moderate inter-subject variability of the PK parameters was observed.
- Stratification of the patients by their CKD sub-stage (3B or 3B-4) for the first time demonstrated an increase in metformin plasma level occurred in the 1000mg dose, highlighting the need for monitoring of patients in usual care to be followed up on their CKD progression especially in stage 2B, where the 1000mg dose represents the highest authorized dose. In these patients, even the 750mg dose increased the concentration in the deep compartment erythrocytes.

12 REFERENCES

1. Ali S, Fonseca V. Overview of metformin: special focus on metformin extended release. *Expert Opin Pharmacother*, 2012 Aug;13(12):1797-805.
2. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care*, 2006 Apr;29(4):759-64.
3. Aggarwal N, Singla A, Mathieu C, Montanya E, Pfeiffer AFH, Johnsson E, Zhao J, Iqbal N, Bailey C. Metformin extended-release versus immediate-release: An international, randomized, double-blind, head-to-head trial in pharmacotherapy-naïve patients with type 2 diabetes. *Diabetes Obes Metab*, 2018 Feb;20(2):463-67.
4. Cullen E, Liao J, Lukacsko P, Niecestro R, Friedhoff L. Pharmacokinetics and dose proportionality of extended-release metformin following administration of 1000, 1500, 2000 and 2500 mg in healthy volunteers. *Biopharm Drug Dispos*, 2004 Sep;25(6):261-3.
5. Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin Pharmacokinet*, 2005;44(7):721-9.
6. Kandhwal K, Dey S, Nazarudheen S, Arora R, Reyar S, Thudi NR, Monif T, Singh MK, Rao S. Pharmacokinetics of a fixed-dose combination of atorvastatin and metformin extended release versus concurrent administration of individual formulations: a randomized, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study. *Clin Drug Investig*, 2011 Dec 1;31(12):853-63.
7. Rhee SJ, Lee S, Yoon SH, Cho JY, Jang IJ, Yu KS. Pharmacokinetics of the evogliptin/metformin extended-release (5/1,000 mg) fixed-dose combination formulation compared to the corresponding loose combination, and food effect in healthy subjects. *Drug Des Devel Ther*, 2016 Apr 13;10:1411-8.
8. Jin X, Kim E, Huh KY, Hwang I, Cho JY, Yu KS, Lee S. Pharmacokinetics and pharmacodynamics of a fixed-dose combination of gemigliptin/metformin sustained release 25/500 mg compared to the loose combination in healthy male subjects. *Transl Clin Pharmacol*. 2020 Mar;28(1):43-54.
9. Lalau JD, Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Belpaire F et al. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. *Diabetes Care*, 2018, 41:547-53.
10. Bergenstal RM, Ahmann AJ, Bailey T, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). *Diabetes Technol Ther*, 2013;15:198-211.
11. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European Association for the Study of Diabetes and the American Diabetes.Association Diabetes Technology Working Group. *Diabetes Care*, 2017;40:1614-21.
12. Lacroix C, Danger P, Wojciechowski F. Microassay of plasma and erythrocyte metformin by high performance liquid chromatography. *Ann Biol Clin (Paris)* 1991, 49:98-101.
13. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. *Comput Methods Programs Biomed*, 2010, 99:306-14.