Nottingham University Hospitals NHS

NHS Trust

END OF STUDY REPORT

21.12.2015

A Study of the antiviral activity of Metformin as an anti-Hepatitis C virus agent in patients with chronic Hepatitis C virus infection

Protocol Number	Version 1 06 September 2010
Chief Investigator	Dr Stephen Ryder
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Name of Test Drug/Investigational Product	Metformin
Indication Studied	Chronic HCV infection

Report Author: [Name] [Title]

Date: 17th September 2015 (DD-MMM-YYYY)

Sponsor Authorisation: Dr. Brian Thomson, Director of Research and Innovation, Nottingham University Hospitals NHS Trust

Date: 22/12/2015 (DD-MMM-YYYY)

This study was carried out in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and Nottingham University Hospitals NHS Trust (NUH) Research and Innovation (R&I) Procedures

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List of Abbreviations and Definition of Terms:

ALT	Alanine aminotransferase
AE	Adverse Event
AMPK	Adenosine 5'-monophosphate (AMP)-activated protein kinase
bd	bis in die 'twice daily'
BRU	Biomedical Research Unit
CI	Chief Investigator
Co-I	Co-investigator
CRF	Case Report Form
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
g	Grams
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HCV	Hepatitis C Virus
HCV RNA	Hepatitis C Viral Ribonucleic acid
HOMA	Homeostasis Model Assessment
ICF IMP	Informed Consent Form Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
NHS	National Health Service
NUH	Nottingham University Hospitals
PI	Principal Investigator
PIS	Participant Information Sheet
QMC	Queens Medical Centre
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Summary of study

HCV infection is a major cause of cirrhosis and liver disease related death worldwide. At the time of study interferon based therapies with cure rate of around 55% were the main stay of treatment for HCV infection. A study limited to patients with genotype 1 HCV infection and demonstrable insulin resistance showed no additional benefit of adding metformin to interferon and Ribivarin therapy on HCV cure rates. Data available from *in vitro* studies from University of Leeds demonstrated that HCV mediated inhibition of enzyme AMPK (Adenosine 5-Mono-phosphate -activated protein kinase) is essential for effective viral replication[1].

Metformin by inducing activation of AMPK results in reciprocal inhibition of HCV replication raising the possibility that metformin may have direct antiviral effect *in vivo*. Metformin is a cheap, readily available drug with excellent side effect profile. Our study aimed to determine if oral metformin therapy has a direct effect on HCV viraemia.

This study was a single-centre, single-arm, open label pilot study. Adult patients with detectable HCV RNA were identified and recruited from patients attending the hepatitis clinic at Nottingham University Hospital NHS Trust, Queens Medical Centre, Nottingham. The study was designed as an open label trial where patients were required to take Metformin therapy twice a day for 2 weeks.

The initial approach was from a physician member of the patient's usual care team (the hepatitis clinic was run by the PI and the Co-I). The investigator or their nominee from the research team informed the participant of all aspects pertaining to their participation in the study and a patient information sheet was supplied. Patients were informed that they had a minimum of 24hrs to decide whether they wish to take part or not and that their decision to take part was entirely voluntary and would not affect the standard of care that they receive. Those who agreed to take part in the trial were given a morning appointment to attend the clinic where

informed consent was obtained by an investigator. The exclusion/inclusion criteria was checked for eligibility. If needed, the usual hospital interpreter and translator services were made available to assist with discussion of the trial, the participant information sheets, and consent forms; but the consent forms and information sheets were not made available printed in other languages. It was also explained that they could withdraw at any time. In the event of their withdrawal it was explained that their data collected so far could not be erased and consent would be sought to use the data in the final analyses where appropriate. Information about the trial was on display in the relevant clinical areas. Patients who were identified in advance from clinic lists were contacted by the PI by letter to invite their participation.

Adult males and females (18-70yrs old) with Chronic HCV infection, able to give consent, were included. Women of child bearing potential (who had a negative pregnancy test) were included if they agreed to use methods of medically acceptable forms of contraception during the study (e.g. intra-uterine device (IUD) or a double-barrier method of oral contraception with condom. Patients with Type 2 diabetes, impaired renal function, de-compensated liver cirrhosis, pregnant females and those, who in the opinion of the Investigator are considered unsuitable, were excluded from the study.

The study included 16 eligible patients infected with HCV. There were 11 males and 5 female. The age range was 39 – 61 years with a mean age of 51 years. Genotypes were identified as Type 1 in ten patients, type 2 in three and type 3 in three patients. HCV RNA levels were checked for all patients at Day 0, Day 7, Day 14 and Day 28, except six patients did not have their HCV RNA levels checked at Day 28. Three of them did not attend the appointment on day 28 and one did not attend from Day 14. One patient missed multiple doses of the trial drug- metformin and one patient took only 1 gram/ day instead of 2 grams / day (in divided doses). Comparative analysis of the data was done using PRISM software. The HCV RNA levels did not show any significant decline with 4 weeks of metformin therapy. We

also measured ALT, Glucose, Insulin and Cholesterol levels at day 0, day 7 and day 14. ALT, Glucose and cholesterol levels were not significantly affected by metformin therapy. None of the patients were known to be diabetic. A significant decline in insulin levels was noted whilst on metformin therapy. No adverse events were reported during the duration of the trail.

2. Objectives

Aim: To test whether administration of Metformin to patients with chronic hepatitis C virus infection results in a reduction in viral load.

PRIMARY OBJECTIVE:

To measure and compare pre-treatment HCV RNA with post-treatment HCV RNA levels.

SECONDARY OBJECTIVES:

Measure Insulin resistance markers (using the Homeostasis Model Assessment – HOMA) at end of week 1 (day 7) and week 2 (day 14) of therapy.

3. Ethical Review

This study was carried out in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and Nottingham University Hospitals NHS Trust (NUH) Research and Innovation (R&I) Procedures. The trial protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department.

4. Investigational Plan

Study design:

Enrolment (Visit 1, Day 0):

All patients that decided to take part in the study were given a morning appointment to attend the clinic for an enrolment visit. They were told to fast overnight from the previous midnight. At the enrolment visit demographics and medical history were taken. Exclusion/Inclusion criteria ware checked and informed consent was taken. Once the patient had consented a 20mL blood sample was taken to test for HCV RNA, ALT, Insulin, Glucose and Fasting lipids- Cholesterol and triglycerides (TGs). Patients were issued with a prescription to take to the NUH Pharmacy for collection of the first 7 days of Metformin treatment and were given a morning appointment to attend visit 2 in 7 days time.

Visit 2 (Day 7):

Patients returned to the clinic after 7 days of treatment having fasted overnight from the previous midnight. A 20mL blood sample was taken to test for to test for HCV RNA, ALT, Insulin, Glucose and Fasting lipids- Cholesterol and TGs. The patients were given a repeat prescription to collect the second weeks' worth of treatment from Pharmacy and were requested to return any unused or leftover treatment and packaging from the previous week to Pharmacy for accountability.

Visit 3 (Day 14):

Patients returned to the clinic after 14 days of treatment having fasted overnight from the previous midnight. A 20mL blood sample was taken to test for HCV RNA, ALT, Insulin, Glucose and Fasting lipids (Cholesterol, TGs).The patient returned any unused or leftover treatment and packaging from the previous week to Pharmacy for accountability and then destruction.

Visit 4 (Day 28):

Those patients whose viral load dropped by >1 log on day 14 were invited back for a 4th visit on day 28. A blood sample was taken for HCV RNA load measurement.

5. Selection of Study Population

Inclusion criteria:

1. Adult males and females (18-70yrs old) able to give consent.
2. Chronic hepatitis C virus infection.
3. Women of child bearing potential (who have a negative pregnancy test) must agree to use methods of medically acceptable forms of contraception during the study; (e.g. intra-uterine device (IUD) or a double-barrier method of oral contraception with condom).

Exclusion criteria:

1. Type 2 diabetes.
2. Patients with impaired renal function.
3. De-compensated liver cirrhosis (stable patients with cirrhosis would be eligible).
4. Patients who in the opinion of the Investigator are considered unsuitable.
5. Pregnant females.

6. Study Settings

The study was an open label study of 2 weeks of oral metformin at a dose of 1g bd based at Nottingham University Hospitals NHS Trust, Queens medical Centre, Nottingham. Patients were recruited via the viral hepatitis clinics based at NUH.

Study team:

1. Dr SD Ryder (PI)
2. Dr M James (Co-I)
3. Dr BJ Thomson (Co-I)
4. Dr Y Taha (Co-I)
5. Sr M Nicholls (BRU research nurse)

7. Interventions

The study was an open label study of 2 weeks of oral metformin at a dose of 1g bd. Metformin Hydrochloride is licensed for the treatment of diabetes mellitus and is commercially available and widely prescribed as a first line agent for the treatment of non-insulin dependent diabetes. The drug, Metformin was being used, 'off-label' in this study.

Metformin tablets 500mg are white, film coated round, biconvex tablets available in blister packs of 28. Other ingredients may include sodium starch glycollate (type A), maize starch, povidone K30, colloidal anhydrous silica, magnesium stearate, methylhydroxypropylcellulose, titanium dioxide E 171, propylene glycol E1520, polyethylene glycol 6000, and purified talc E553 b. Commonest known Side Effects include anorexia, nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.

These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. Abdominal pain, taste decreased vitamin-B12 absorption, erythema, pruritis, urticaria and hepatitis and lactic acidosis have also been reported. Renal impairment increases the risk of lactic acidosis

A supply for use in the study was identified, stored in a controlled, temperature monitored environment and dispensed in accordance with a trial prescription from the NUH QMC clinical trials pharmacy. Receipt of IMP into pharmacy, issue to trial subjects and details of unused IMP returned to pharmacy were recorded on trial specific accountability documents in pharmacy. IMP destruction was recorded following completion of accountability.

Patients were issued with a prescription on Day 0 to take to the NUH QMC Pharmacy for collection of the first 7 days of Metformin treatment and were given a morning appointment to attend visit 2 in 7 days time. The patients were given repeat prescription at Day 7 to collect the second weeks' worth of treatment from Pharmacy and were requested to return any unused or leftover treatment and packaging from the previous week to Pharmacy for accountability.

8. Changes in the Protocol from Initial Approval

Changes in the protocol are listed below:

Amendment number	Substantial/Minor	Reason for Amendment
1	Minor	Sponsor was listed as University of Nottingham instead of Nottingham University Hospital NHS Trust
2	Substantial	Change to generic Metformin instead of branded due to supply issues.

9. Protocol Deviations

HCV RNA levels were checked for all patients at day 0, day 7, day 14 and day 28, however six patients did not have their HCV RNA levels checked at Day 28. Three patients did not attend their appointment on Day 28 and one patient did not attend from Day 14. One patient missed multiple doses of the trial drug metformin and one patient took only 1g/day instead of 2g /day (in divided doses).

10. Patient Information & Consent

All participants provided written informed consent (**Appendices**). The Informed Consent Form was signed and dated by the participant before they enter the trial. The Investigator explained the details of the trial and provided a Participant Information Sheet (**Appendices**), ensuring that the participant had sufficient time to consider participating or not. The Investigator answered any questions that the participant had concerning study participation.

Informed consent was collected from each participant before they underwent any interventions (including physical examination and history taking) related to the study. One copy of the consent was given to the participant, one was kept by the Investigator, and a third was retained in the patient's hospital records.

11. Safety Reporting

No safety events were identified

12. Statistical Analysis

Sample size justification:

As a pilot study, a formal sample size estimate based on power has not been performed. However a sample of 30 individuals will enable the percentage of responders to be identified to within +/-18 percentage points at worst; while a sample of 30 is also reasonable to estimate the mean and shape of the distribution of changes in viral load.

Study populations:

Safety set: All randomised participants who received at least one dose of the study drug.

Full Analysis set: All participants, who took at least one dose of study medication and for whom at least one post-baseline assessment of the primary endpoint is available.

Per protocol set: All participants in the Full Analysis set who were deemed to have no major protocol violations that could interfere with the objectives of the study.

Methods :

Assessment of efficacy: Percentage of patients demonstrating a <1 log drop in HCV viral load, with 95% confidence limits. Distribution of changes in viral load summarised graphically and in terms of mean, median, and interquartile range.

Assessment of safety: frequency of patient recorded adverse events.

Comparative analysis of data was done using PRISM software.

13. Main Findings of the Study

The HCV RNA levels did not show any significant decline with 4 weeks of metformin therapy (**Figure 1 and Figure 2**). ALT, Glucose and cholesterol levels were not significantly affected by metformin therapy (**Figure 3, Figure 4 and Figure 5**). None of the patients were known to be diabetic. A significant decline in insulin levels was noted whilst on metformin therapy (**Figure 6**). No adverse events were reported during the duration of the trail.

14. Conclusions

We conclude that Metformin failed to show any significant anti-retro-viral activity with 4 weeks of therapy in patients with chronic HCV infection. It seems that metformin has little potential role as a therapeutic agent particularly given the recent approvals of a number of highly effective drugs targeting viral proteins.

15. References

1 Mankouri J, Tedbury PR, Gretton S, Hughes ME, Griffin SD, Dallas ML, Green KA, Hardie DG, Peers C, Harris M. Enhanced hepatitis C virus genome replication and lipid accumulation mediated by inhibition of AMP-activated protein kinase. Proc Natl Acad Sci U S A. 2010 Jun 22;107(25):11549-54. doi: 10.1073/pnas.0912426107. Epub 2010 Jun 7. PubMed PMID: 20534540; PubMed Central PMCID: PMC2895084.

16. Appendices

Winthrop Pharmaceuticals UK Ltd
One Onslow Street, Guildford, Surrey, GU1 4YS, UK
Telephone: +44 (0)1483 505 515
Fax: +44 (0)1483 554 831
E-mail: UK-medicalinformation@sanofi-aventis.com
Medical Information Direct Line: +44 (0)1483 554 101
Medical Information Fax: +44 (0)1483 554 831

Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 04/10/2010

Metformin 500mg tablets

Table of Contents

1. NAME OF THE MEDICINAL PRODUCT

Metformin 500mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains:

Metformin hydrochloride 500 mg

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White, biconvex, round, film-coated tablets, embossed S137 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

• In adults, Metformin film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.

• In children from 10 years of age and adolescents, Metformin film-coated tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure (see 5.1. "Pharmacodynamic properties").

4.2 Posology and method of administration

Adults

Monotherapy and combination with other oral antidiabetic agents:

• The usual starting dose is one tablet 2 or 3 times daily given during or after meals.

• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 3 g daily.

• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin is given at the usual starting dose of one tablet 2-3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly: due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4 “Special warnings and precautions for use”).

Children and adolescents

Monotherapy and combination with insulin:

• Metformin film-coated tablets can be used in children from 10 years of age and adolescents.

• The usual starting dose is one tablet of 500 mg or 850 mg once daily, given during meals or after meals.

• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

•

• Hypersensitivity to metformin hydrochloride or to any of the other excipients

• Diabetic ketoacidosis, diabetic pre-coma

• Renal failure or renal dysfunction (e.g., serum creatinine levels> 135 μmol/L in males and> 110 μmol/L in females)

• Acute conditions with the potential to alter renal function such as:

- dehydration

- severe infection

- shock

• Intravascular administration of iodinated contrast agents (see 4.4 “Special warnings and precautions for use”)

• Acute or chronic disease which may cause tissue hypoxia such as:

- cardiac or respiratory failure

- recent myocardial infarction

- shock

• Hepatic insufficiency, acute alcohol intoxication, alcoholism

• Lactation

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9 “Overdose”).

Renal function:

As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

* at least annually in patients with normal renal function,

* at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent:

As the intravascular administration of iodinated contrast materials in radiologic studies

can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery:

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Children and adolescents:

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although metformin efficacy and safety in children below 12 did not differ from efficacy and safety in older children, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:

• All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

• The usual laboratory tests for diabetes monitoring should be performed regularly.

• Metormin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulphonylureas.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Alcohol:

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

• fasting or malnutrition

• hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents (see section 4.4 "Special warnings and precautions for use"):

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

4.6 Pregnancy and lactation

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development (see also section 5.3 "Preclinical safety data").

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, insulin, repaglinide).

4.8 Undesirable effects

The following undesirable effects may occur with Metformin.

Frequencies are as follows:

Very common: 1/10

Common: 1/100 to <1/10

Uncommon: 1/1000 to <1/100

Rare: 1/10,000 to <1/1000

Very rare: <1/10,000

Gastrointestinal Disorders:

Very common: Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Nervous system disorders:

Common: Taste disturbance

Metabolism and nutrition disorders:

Very rare: Decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.

Lactic acidosis is very rare (see 4.4 “Special warnings and precautions for use”).

Skin and subcutaneous tissue disorders:

Very rare: Skin reactions such as erythema, pruritus, urticaria

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Hepatobiliary disorders:

Isolated reports: Liver function test abnormalities or hepatitis resolving upon metformin discontinuation .

4.9 Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral blood glucose lowering drugs, A10B A02

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation (3) and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

• a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034.

• a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;

• a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);

• a significant reduction in the absolute risk of myocardial infarction: metformin 11

events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of metformin, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 4 μg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is> 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal

elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Paediatrics:

Single dose study: After single doses of metformin 500 mg, paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg BID for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg BID for 14 days. As the dose is individually titratedbased on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Sodium starch glycollate

Maize starch

Povidone

Colloidal anhydrous silica

Magnesium stearate

Film-coating

Methylhydroxypropylcellulose

Titanium dioxide E 171

Propylene glycol

Macrogol 6000

Purified talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Blister packs of 28, 84, 300 and 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Winthrop Pharmaceuticals UK Limited

One Onslow Street

Guildford

Surrey

GU1 4YS

UK

8. MARKETING AUTHORISATION NUMBER(S)
PL 17780/0080

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01 October 2001

10. DATE OF REVISION OF THE TEXT
15 September 2008

The University of Nottingham

Nottingham University Hospitals NHS Trust

Patient Information Sheet
Metformin therapy in HCV infection

You are being invited to take part in a research study. Before you decide, you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The purpose of this study is to look at whether the drug Metformin, commonly used to treat type II diabetes can lower viral load in patients with chronic Hepatitis C virus (HCV) infection.

Background
HCV is a worldwide infection and one of the major causes of liver disease.
Current treatments with Interferon and ribavirin combination therapy result in cure rates of around 50-55% which leaves a significant number of patients without an effective therapy.
Some treatments still in the developmental stages have so far proved to be toxic or potentially extremely costly giving rise to the need to look for potential alternatives.
Laboratory studies have shown that metformin can inhibit (slow down) the rate at which HCV multiplies, (this can be measured by a drop in viral load **- viral load can be tested for using a sample of blood and measures the amount of virus in the blood which indicates the level of infection).**
In this pilot study we would like to see if Metformin treatment does indeed result in a drop in viral load and be able to measure this.

Why have I been chosen?
We are inviting you to help us in this research because you have HCV infection.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw consent at any time, without giving a reason and can do this simply by informing the researcher whose contact details are at the end of this leaflet.
A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
The study will involve you taking two 500mg Metformin tablets, twice daily for two weeks, (you will therefore take a total of 4 tablets per day). You will also be required to visit the hospital up to 4 times over a period of 4 weeks and give a 20ml blood sample each time (equivalent to 4 teaspoonfuls). You will be required to fast overnight from the previous midnight before each of your first 3 appointments.

Visit 1(enrolment):
You will arrive for a morning appointment after an overnight fast. We will check your eligibility for the study against the inclusion/exclusion criteria list and ask you for information on demography and medical history. If you are suitable for the study then informed consent will be taken.
We will then take a blood sample and you will be issued with a prescription (you will be required to take this to the hospital pharmacy, who will issue you with the first 7 days supply of Metformin treatment.)
At the end of your visit we will arrange with you, your visit 2 appointment date.

Visit 2 (Day 7):
You will return to the clinic after taking 7 days of Metformin treatment and having fasted from the previous midnight.
A 20ml blood sample will be taken and you will be issued with a second prescription for 7 days worth of Metformin treatment and an appointment will be arranged for your next visit.

Visit 3: (Day 14):
You will return to the clinic after having completed 2 weeks of Metformin therapy and having fasted from the previous midnight.
A 20ml blood sample will be taken.

Visit 4: (Day 28):
We *may contact you after your 3rd visit to ask you to return for another visit - visit 4 on day 28. This will NOT require an overnight fast. The purpose of this visit will be to take a final blood sample of just 10mls (2 teaspoonfuls)
Please note that you will only be invited to return for the 4th visit on Day 28, if your visit 3 (Day 14) blood tests have shown a significant drop in viral load since Day 0. Those patients whose drop in viral load is less than this will therefore not be re-contacted and visit 3(Day 14) will be considered your final visit.

Deleted: *(For the purposes of this research project we will be looking for a drop greater than 1 log.).*

What will happen to any samples I give?
We will separate the fluid part of your blood (serum) from the cells and analyse it for HCV levels and other factors such as glucose & insulin levels.
With your permission we would like to store and use the serum in other future studies (this is indicated on your consent form). At present, we do not know what those studies will be, but this is a research field of great importance and interest, and the availability of well-characterised plasma samples from the groups of patients outlined above is a potentially valuable resource for future research. Such future studies may be conducted by, our-selves, or they may be in collaboration with other research groups, including those within commercial organisations, and research groups outside the UK. As indicated above; it will not be possible for any future research collaborators to identify from whom the samples originated.

What will happen if I don't want to carry on with the study?
You are free to withdraw from the study at any time without having to give a reason.
If you withdraw from the study, we will destroy all your identifiable samples but we will need to use the data collected up to your withdrawal.

What are the possible disadvantages and risks of taking part?
-Taking blood samples can cause temporary discomfort and temporary bruising.
-Metformin may cause nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.
These effects can occur during initiation of therapy and resolve spontaneously in most cases.

What are the possible benefits of taking part?
There is no immediate clinical benefit to you from taking part in the research.
However we hope that the information and results obtained will enable us to go on to be able to conduct a Phase III Clinical Trial based on Standard Therapy alone versus Standard Therapy in addition to Metformin in the future.
Please note, that Metformin will not be available once your participation in the trial stops (even if it may have proven effective for you.)
What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decided not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he/she may ask you to sign an updated consent form.

If this happens, your research doctor might consider you should withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

Participant stipends and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any hospital visits in excess of usual care.

What if there is a problem?
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of this study, you should ask to speak to one of the researchers who will do their best to answer your questions. If you have a complaint, (for example on your treatment by a member of staff) you can initially approach the lead investigator Dr Stephen Ryder.

If you still remain unhappy and wish to complain formally, the normal *National Health Service complaints procedure or NHS Patient Advice & Liaison Service (PALS)* office is available to you and can be contacted *on Free phone: 0800 183 0204 or via the helpdesk, Main entrance Queens Medical Centre.*

Will my taking part in this study be kept confidential?
Yes. All information which is collected about you during the course of the research will be kept strictly confidential. Your medical records may be inspected by the research team for purposes of analysing the results. Your name, however, will not be disclosed outside the hospital. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

With your permission we will notify your GP of your participation in the trial.

What will happen to the results of the research study?
We anticipate that the results of the study will be published in a scientific journal and will be presented at scientific meetings.
You and your details will remain strictly confidential and you will not personally be identified in any report or publication.

Who is organising and funding the research?
This study is being organised by The Nottingham University Hospitals NHS Trust and funded by The Nottingham University Hospitals NHS Trust Charitable Funds Research Award.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights well being and dignity.
This study has been reviewed and given favourable opinion by, **Leicestershire, Northamptonshire and Rutland Research Ethics Committee 1**

Who do I contact for further information on this study?

Dr Stephen Ryder **(Chief Investigator)**
Diagnostics & Clinical support Directorate
Nottingham University Hospitals NHS
Queens Medical Centre Campus
Nottingham,
NG72UH.
Telephone: 0115 9249924 ext. 663443
Email: Stephen.ryder@nuh.nhs.uk

Professor Will Irving
Dept. Microbiology
Nottingham University Hospitals NHS
Queens Medical Centre Campus
Nottingham
NG72UH.
0115 8230752
Email:will.irving@nottingham.ac.uk

Thank you for reading this information sheet.

Deleted: ¶

Nottingham University Hospitals NHS
NHS Trust

NDDC Nottingham Digestive Diseases Centre
BRU Biomedical Research Unit

Participant ID ☐☐☐

PATIENT CONSENT FORM

Metformin Therapy in HCV infection

Name of Investigator: Dr. Stephen Ryder **Please initial box**

1. I confirm that I have read and understand the patient information sheet dated **20/10**/2010 (version **1.1**) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from the Nottingham University Hospitals NHS Trust, the research group, the REC and the MHRA, where it is relevant to my taking part in this study. ☐
4. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
5. I agree to provide blood samples for analysis during this current study. ☐
6. I give permission to inform my GP of my participation in the study. ☐
7. I agree that at the end of this study, my serum samples may be stored for possible use in other future studies. ☐
8. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

1 copy for the patient, 1 copy to be placed in the medical notes and 1 copy for the study file.

The University of Nottingham

Nottingham University Hospitals NHS
NHS Trust

Dr S Ryder, Clinical Director
University of Nottingham
Queens Medical Centre
Nottingham
NG7 2UH
Tel: 0115 8231030

Dear Colleague,

Study Title: Metformin Therapy in HCV infection

This is to inform you that your patient:

Name: _____

DOB: _____

has agreed to take part in a clinical study to look at whether 2 weeks of Metformin treatment (1g bd.) results in a drop in viral load (by at least 1 log) in patients with chronic HCV.

A Patient information sheet has been enclosed for your information.
If you have any concerns, please contact me at the above address.

Yours sincerely

Dr Stephen Ryder

The University of Nottingham

Nottingham University Hospitals NHS
NHS Trust

Dr S Ryder, Clinical Director
Diagnostics & Clinical Support Directorate
Nottingham University Hospitals NHS Trust
Queens Medical Centre Campus
Derby Road
Nottingham
NG7 1HT
Tel: 0115 9249924 ext.63443

Dear,

We are writing to you to inform you of a research study which we will be carrying out in patients with HCV.

There is absolutely no obligation to take part but we would be grateful if you would take the time to read the enclosed information sheet, and consider helping us.

One of our research nurses will contact you in the next few days to check that you have received this information, answer any questions you may have and discuss whether you would be interested in taking part.

In the meantime, if the enclosed information has explained all you need to know at this stage and you have decided that you would like to take part in this study please contact us using the contact details on the Information sheet.

Thank you for taking the time to read the enclosed documents,

Yours sincerely

Dr Stephen Ryder

A study of the antiviral activity of Metformin as an anti-Hepatitis C virus agent in patients with chronic Hepatitis C virus infection

Enrolment (Visit 1, Day 0) Form 1

Patient Study Number: _____ Patient initials: _____ Date of birth: _____

Date of Study Visit:						
Patient eligibility:						
Inclusion			Exclusion			
Adult Male and Female (18-70 yrs old) and able to give consent	*Yes* ☐	*No* ☐	Type 2 diabetes	*Yes* ☐	*No* ☐	
Chronic hepatitis C virus infection:	*Yes* ☐	*No* ☐	Impaired renal function	*Yes* ☐	*No* ☐	
Women of child bearing potential & willing to use medically acceptable forms of contraception:	*Yes* ☐	*No* ☐	Decompensated liver cirrhosis (stable patients with cirrhosis would be eligible)	*Yes* ☐	*No* ☐	
Currently not on treatment:	*Yes* ☐	*No* ☐	Pregnant women:	*Yes* ☐	*No* ☐	
If any of the above shaded boses are checked, patient is ineligible						
Medical History:						
Is patient of child-bearing potential?	Yes	☐	No	☐	N/A	☐
Pregnancy test done?	Yes	☐	No	☐	N/A	☐
Result of pregnancy test:						
Treatment naïve /has had previous course of therapy:						
Has the patient had a liver biopsy?			Yes ☐		No ☐	
If yes : date of liver biopsy:						

Confirm visit has taken place:	Signature:	Date:

Name of person completing form (Capitals): _____

Signature of person completing form: _____ Date (dd/mm/yy) _____

Checked by: _____

A study of the antiviral activity of Metformin as an anti-Hepatitis C virus agent in patients with chronic Hepatitis C virus infection

Enrolment (Visit 1, Day 0) Form 1

Patient Study Number: _____ Patient initials: _____ Date of birth: _____

What was the NI Grade and fibrosis stage:
Height:
Weight:
BMI:
Waist circumference:
Current prescribed medications:

Drug:	Dose:	Frequency	Start
Drug:	Dose:	Frequency	Start
Drug:	Dose:	Frequency	Start
Drug:	Dose:	Frequency	Start
Drug:	Dose:	Frequency	Start
Drug:	Dose:	Frequency	Start

Does the patient meet the eligibility criteria? Yes ☐ No ☐

Confirm visit has taken place:	Signature:	Date:

Name of person completing form (Capitals): _____

Signature of person completing form: _____ Date (dd/mm/yy) _____

Checked by: _____

A study of the antiviral activity of Metformin as an anti-Hepatitis C virus agent in patients with chronic Hepatitis C virus infection

Enrolment (Visit 1, Day 0) Form 1

Patient Study Number: _____ Patient initials: _____ Date of birth: _____

Does the patient consent to take part in this study?	Yes ☐	No ☐

Results:	
Genotype:	
Result:	Comment:
HCV RNA Viral Load:	
Result:	Comment:
ALT: (Range: Female Up to 35U/L, Male Up to 45U/L)	
Result:	Comment:
Insulin: (Range: 6-25 mU/L)	
Result:	Comment:
Glucose: (Range: Fasting 3.0 – 6.0 mmol/L)	
Result:	Comment:
Cholesterol:	
Result:	Comment:

Confirm visit has taken place:	Signature:	Date:

Name of person completing form (Capitals): _____

Signature of person completing form: _____ Date (dd/mm/yy) _____

Checked by: _____

A study of the antiviral activity of Metformin as an anti-Hepatitis C virus agent in patients with chronic Hepatitis C virus infection

Enrolment (Visit 1, Day 0) Form 1

Patient Study Number: _____ Patient initials: _____ Date of birth: _____

Triglycerides: (Range: Fasting Female 0.4 – 1.53 mmol/L , Fasting Male 0.45 – 1.81mmol/L)	
Result:	Comment:

(Clinical Chemistry normal ranges obtained Chemical Pathology Service Directory, November 2009, version 3)

GP Letter sent out:	
Photocopy of letter filed in patient notes?	
Prescription issued:	

Confirm visit has taken place:	Signature:	Date:

Name of person completing form (Capitals): _____

Signature of person completing form: _____ Date (dd/mm/yy) _____

Checked by: _____

For Clinical Trial Use Only Eudract No:2010-xxxxxx-xx

Metformin therapy in HCV infection

Metformin Tablets 500mg

Take TWO tablets TWICE daily with meals, for TWO weeks, as directed.

Subject Name Date of dispensing

Subject Study Number xxx

Investigator: Dr S Ryder Nottingham University Hospitals NHS Trust 01159249924 extn

Issued from Pharmacy Department Nottingham University Hospitals NHS Trust QMC Campus

This label to be used on an original pack of licensed medication.

Figure 1 Viral loads with 10 patients

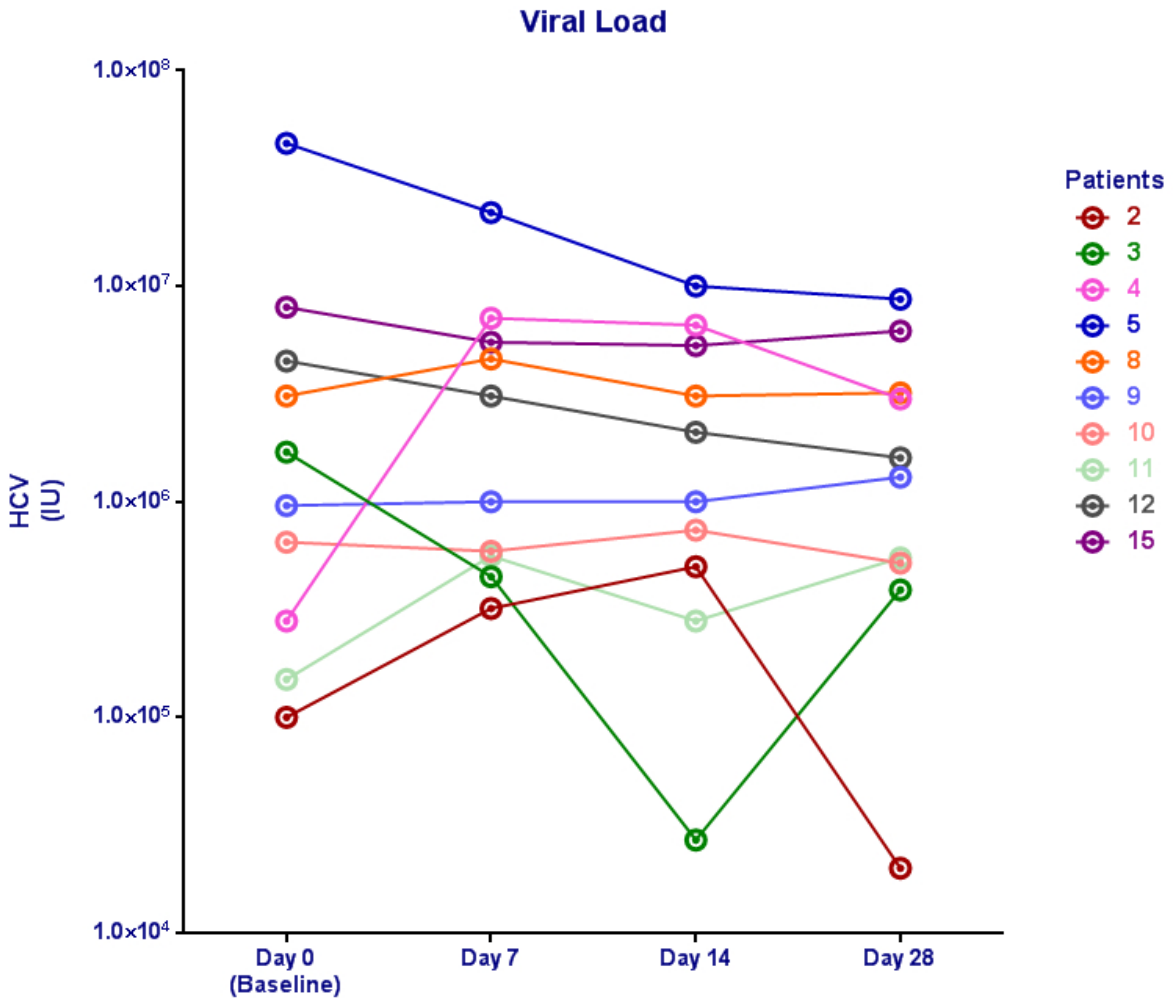

Figure 2 Viral loads with 16 patients

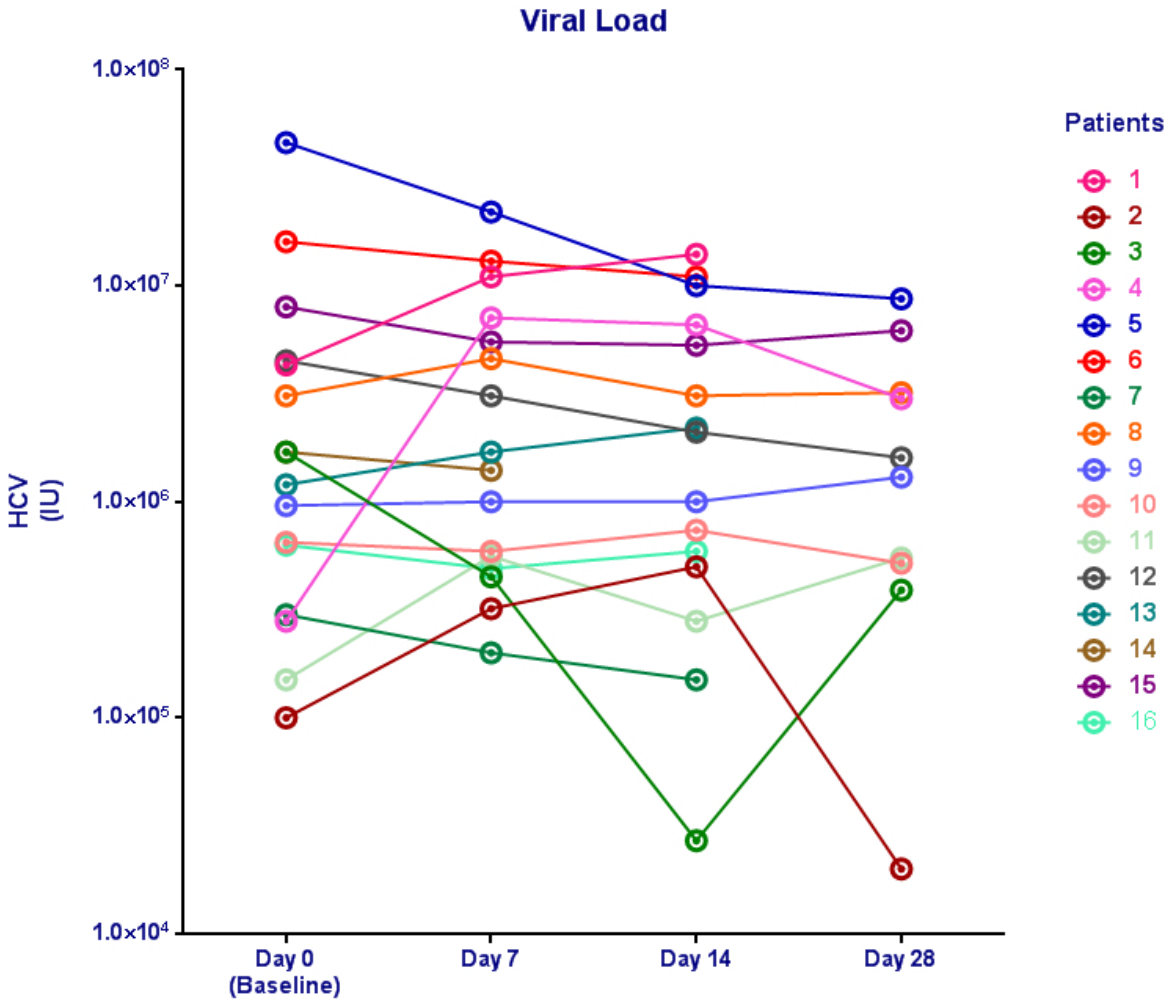

Figure 3 ALT levels

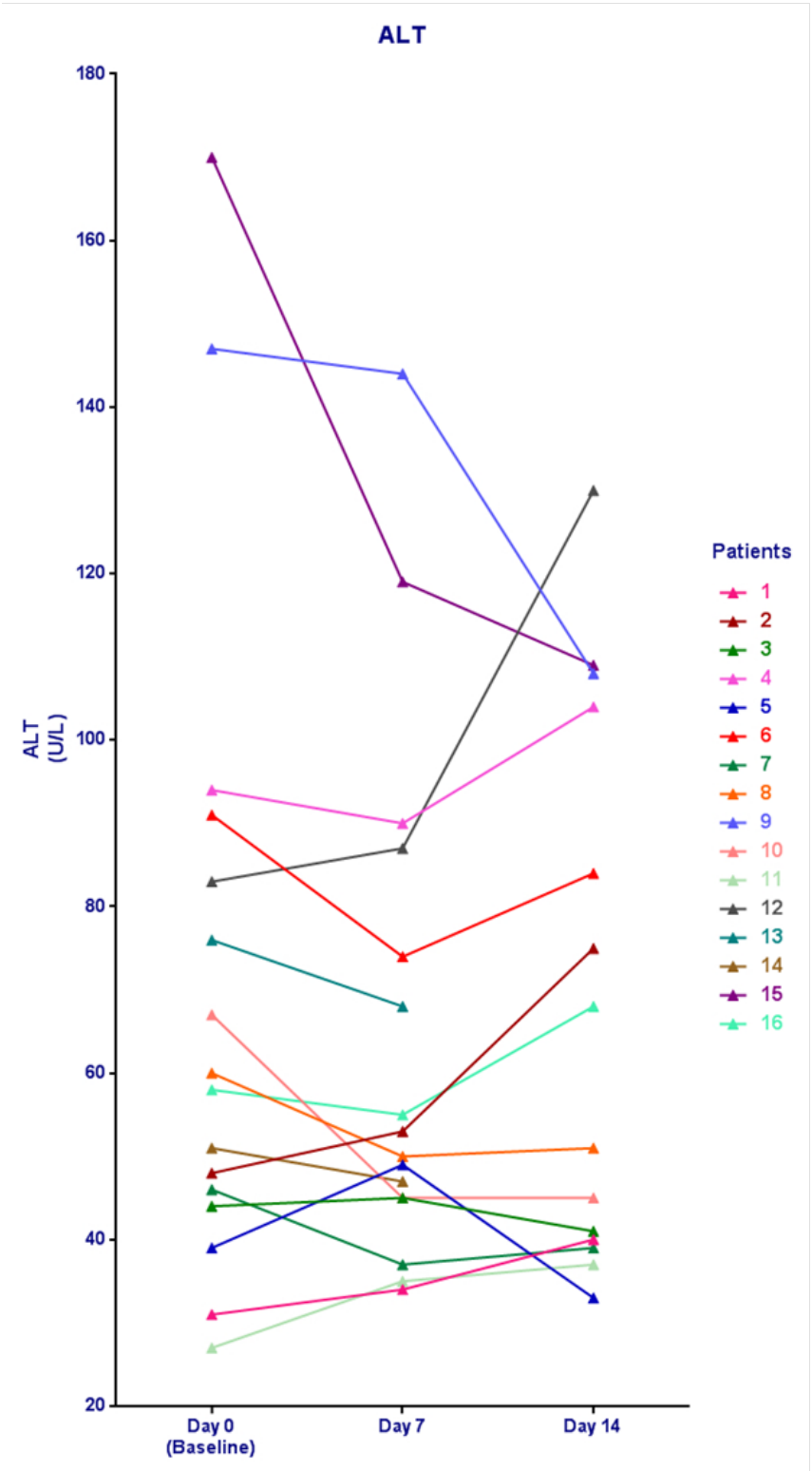

Figure 4 Glucose Levels

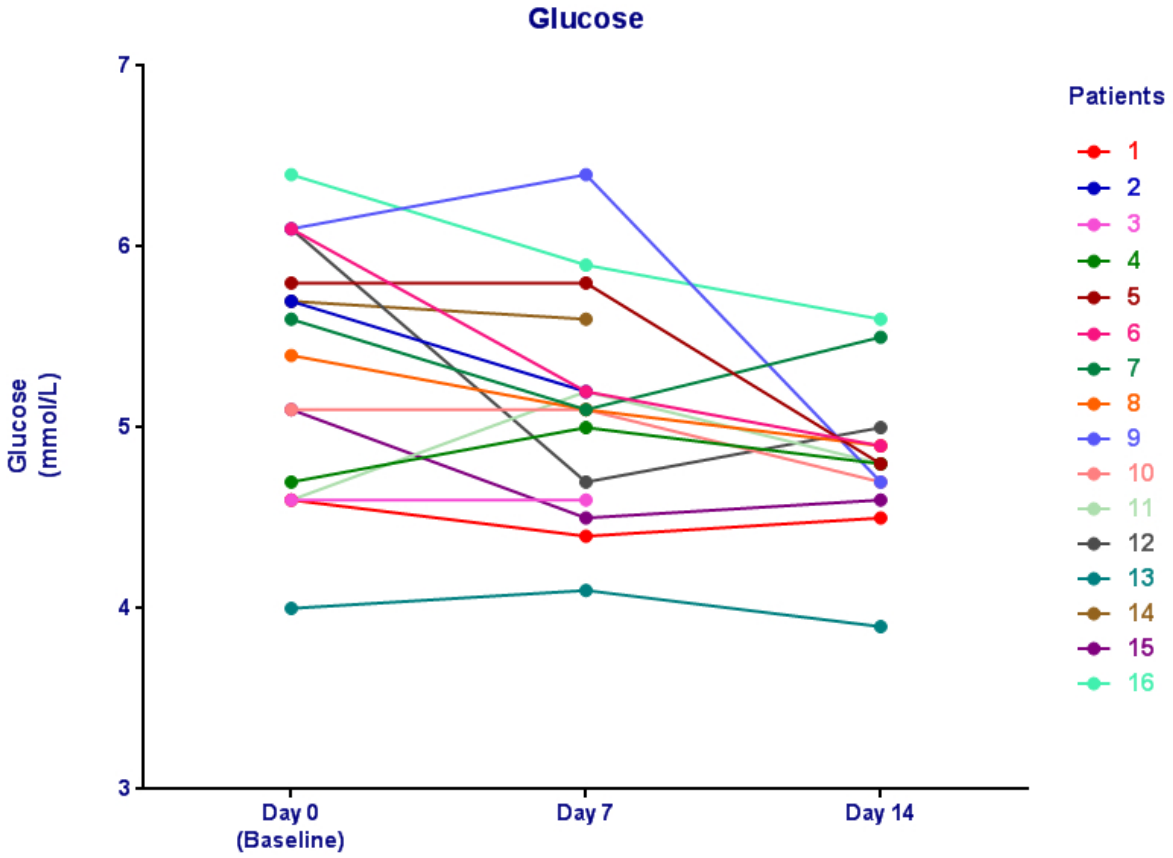

Figure 5 Cholesterol Levels

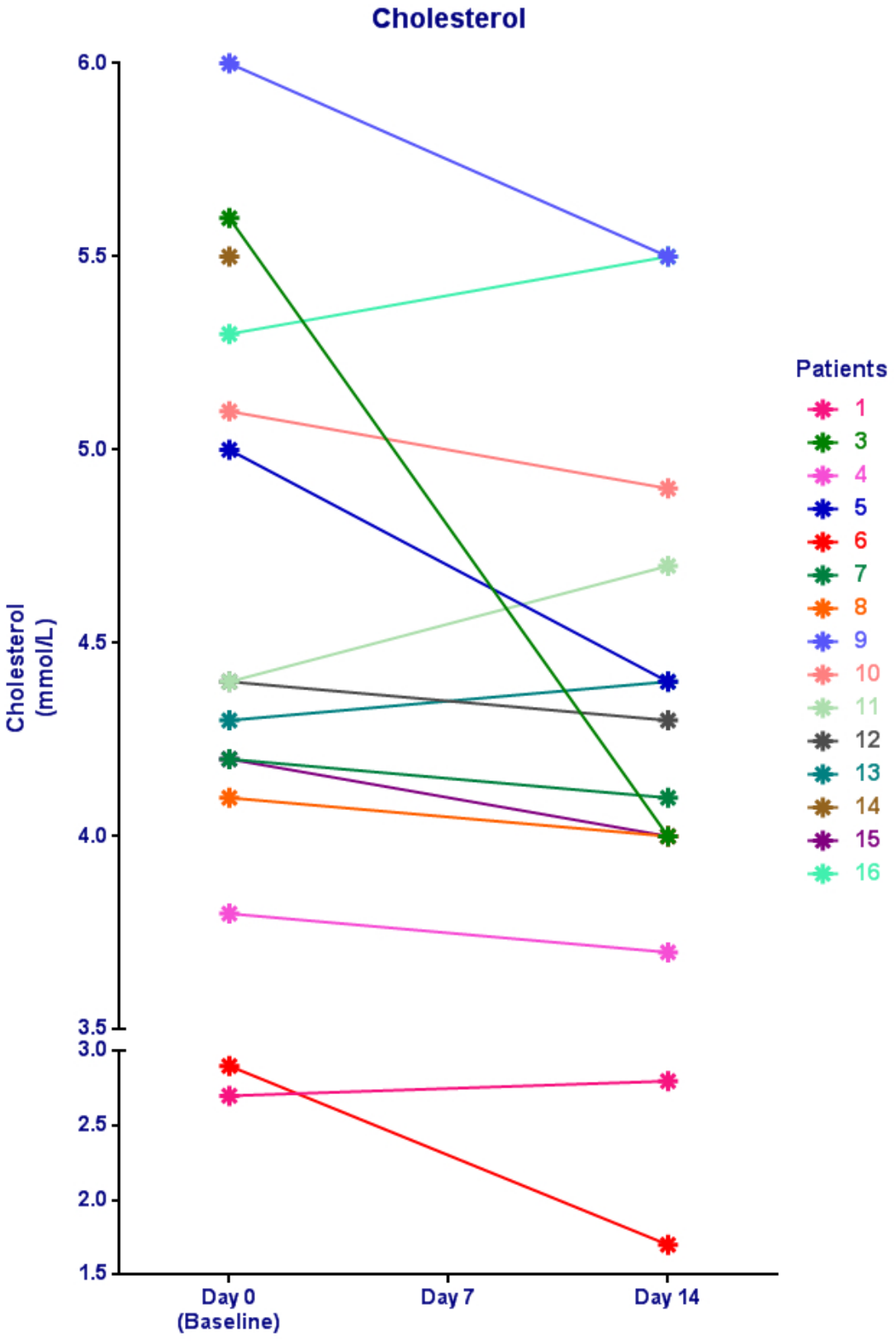

Figure 6 Insulin levels