1. Title Page

Study Title	A Single Arm, Multicenter Study Evaluating Pazopanib in First-line Treatment of Poor-Risk Patients with Locally Advanced or Metastatic Renal Cell Carcinoma
Study Title German	Einarmige, multizentrische Studie zur Bewertung von Pazopanib als Erstlinientherapie in Hochrisikopatienten mit fortgeschrittenem oder metastasierendem Nierenzellkarzinom
Short Title	FLIPPER – **F**irst-**Li**ne **P**azopanib in **P**oor-Risk Patients with M**e**tastatic **R**enal Cell Carcinoma
Protocol No.	IOM-605
EudraCT No	2011-001138-40
Name of test drug/product	Pazopanib/Votrient® - ATC-Code L01XE11
Comparator	N/A
Dosage (strength)	800 mg/day (2 x 400 mg, orally)
Indication	Locally advanced or metastatic renal cell carcinoma
Design	Single arm, open-label, prospective, multicenter, national
Development phase	Phase IV
Sponsor	iOMEDICO, Freiburg, Germany
Coordinating investigator	Prof. Dr. med. Michael Staehler, Munich, Germany
Author of report	iOMEDICO AG
Marketing Authorization Holder / Number	Novartis Europharm Limited / EU/1/10/628/003 - 004
Study initiation date	January 2012
Study completion date	31-Jul-2017
Version and date of report	Final Version 1.0 dated 23-Jan-2018

2. Synopsis

Name of Sponsor/Company: iOMEDICO	Volume: Page:	(For National Authority Use Only)
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Name of Active Ingredient: Pazopanib		

Title of study:
A Single Arm, Multicenter Study Evaluating Pazopanib in First-line Treatment of Poor-Risk Patients with Locally Advanced or Metastatic Renal Cell Carcinoma

Coordinating investigator:
Prof. Dr. Michael Staehler
Ludwig-Maximilians-UniversitätMünchen
Klinikum Großhadern - Urologische Klinik und Poliklinik
Marchioninistr. 15
81377 München
Tel.: +49 89 7095-3722
michael.staehler@med.unimuenchen.de

Study center(s):
Ten Study centers in Germany participated in this study. Out of those 6 sites included patients.

	Center (Name)	Department	Zip Code	City / District	Number of included patients
1	University Frankfurt	Hematology & Oncology	60xxx	Frankfurt a.M.	1
2	Hospital Kassel	Urology	34xxx	Kassel	3
3	Hospital St. Marien	Urology	91xxx	Erlangen	0
4	Hannover Medical School	Hematology, Hemostasis, Oncology and Stem Cell	30xxx	Hannover	4
5	University Münster	Urology	48xxx	Münster	6
6	MVZ Osthessen	Hematology & Oncology	36xxx	Fulda	0
7	University Greifswald	Urology	17xxx	Greifswald	0
8	University Essen	Urololgy	45xxx	Essen	7
9	Ludwig-Maximilians-University (LMU) Munich, Großhardern	Urology	81xxx	Munich	39
10	University Würzburg	Urology	97080	Würzburg	0

Publication (reference):
n.a.

Studied period (years): 2012 to 2017	**Phase of development**: IV

Objectives:
Primary objective:

- To evaluate the efficacy of pazopanib as first-line treatment for poor-risk patients with locally advanced or metastatic renal cell carcinoma (RCC) by assessing the proportion (exact rate) of

Name of Sponsor/Company: iOMEDICO	Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Pazopanib (Votrient®)		
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patients free of progression or death due to progression at 6 months (26 weeks ±7 days) after start of therapy.

Secondary objectives:

- Efficacy (overall survival (OS), progression-free survival (PFS), objective response rate (ORR), duration of response (DOR))
- Safety

Exploratory objectives (not part of this report)**:**

- Biomarker project
- DCE-MRI project

Methodology:

This study was a single arm, open-label, prospective, multicenter, national phase IV study in patients with locally advanced or metastatic RCC (mRCC) and poor-risk features treated with first-line pazopanib.

Number of patients	**planned**: 80 **screened**: 60	**randomized**: n.a. **completed**: 37	**analyzed efficacy**: 34 **analyzed safety**: 43

Diagnosis and main criteria for inclusion:

1. Histologically confirmed metastatic or locally advanced (defined as non-operable tumor), predominantly clear cell RCC.
2. At least three of the following five predictors of short survival are required:
   - Serum lactate dehydrogenase (LDH) > 1.5 x ULN (upper limit of normal)
   - Hemoglobin < LLN (lower limit of normal)
   - Corrected serum calcium level > 10 mg/dL (2.5 mmol/L)
   - Time from diagnosis of RCC to occurrence of metastases of less than 1 year
   - Karnofsky Status of 60 or 70
3. Karnofsky Status ≥ 60
4. Age ≥ 18 years or legal age of consent if greater than 18 years.
5. Dated and signed written informed consent prior to performance of study-specific procedures or assessments.
6. Patients with at least one measurable disease, as defined by RECIST 1.1 (Eisenhauer et al., 2009).
7. Fresh or archived tumor tissue should be provided for all subjects for biomarker analysis before or during treatment with pazopanib.
8. Adequate organ system function as defined as:
   - Hematologic:
     - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
     - Hemoglobin ≥ 9 g/dL (5.6 mmol/L)
     - Platelets ≥ 100 x 10^9/L
     - Prothrombin time or International Normalized Ratio (INR) ≤ 1.2 x ULN
     - Activated partial thromboplastin time (aPTT) ≤ 1.2 x ULN
   - Hepatic:
     - Total bilirubin ≤ 1.5 x ULN
     - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN
   - Renal:

Name of Sponsor/Company: iOMEDICO	Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Pazopanib (Votrient®)		
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- Serum creatinine ≤ 2.5 mg/dL OR, if > 2.5 mg/dL: calculated creatinine clearance (CICR) (appropriate appendix) ≥ 30mL/min
- Urine Protein to Creatinine Ratio (UPC) < 1¸ if UPC ≥ 1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value < 3 g to be eligible.

- Thyroid:
  - Thyroid-stimulating hormone (TSH) within the normal range of the local laboratory

    Note: Patients with hypothyroidism have to be treated according to the clinical standard before pazopanib treatment start.

9. Subjects may not have had a transfusion within 7 days of screening assessment.
10. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
11. Concomitant elevations in bilirubin and AST or ALT above 1.0 x ULN are not permitted. Patients with Gilbert's disease and elevation of indirect bilirubin only can be considered like patients with normal bilirubin.
12. Compliance of the patient.

Test product, dose and mode of administration, batch number:
Pazopanib 800 mg/day (2 x 400 mg, orally) until progression or intolerable toxicity.

Duration of treatment:
Duration of treatment until progression or intolerable toxicity

Reference therapy, dose and mode of administration, batch number:
n.a.

Criteria for evaluation:

Efficacy:

Primary endpoint

- 6-month PFS rate (exact): Proportion of patients free of progression at 6 months (26 weeks ±7 days) after start of first-line therapy with pazopanib. The analysis includes all patients that received at least one dose of pazopanib and which are assessable with regard to their disease status at 26 weeks ±7 days (or before in case of progressive disease (PD) prior to 26 weeks ±7 days after therapy start).

Secondary endpoints:

- OS defined as time from first application of pazopanib to death of any cause. Patients alive at the end of the study were censored with the date of the last contact to the patient
- PFS defined as time from first application of pazopanib to progression (PD according to RECIST 1.1) or death of any cause before start of new antineoplastic treatment. Patients without PD or death were censored at their last date of tumor evaluation.
- ORR was defined as complete response (CR) or partial response (PR) and only to be evaluated as CR or PR if the first finding was confirmed at least 4 weeks later by CT or MRI scan.
- DOR was calculated as the time from first occurrence of a response (at least PR) to a documented PD. If a patient did not experience PD prior to onset of a subsequent therapy the time was censored at last date of tumor evaluation or start of new antineoplastic treatment, whatever came first. The analysis was only conducted for patients with response (at least PR).

Safety:

- Assessment of safety profile of pazopanib in first-line poor-risk patients
- Medical History

Name of Sponsor/Company: iOMEDICO	Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Pazopanib (Votrient®)		
Name of Active Ingredient: Pazopanib		

- Physical examination
- Vital signs: Resting blood pressure, pulse rate, weight
- Karnofsky Performance Status
- Extent of pazopanib exposure
- Treatment modifications
- Clinical laboratory:
  - Electrolytes: Sodium, potassium, calcium, magnesium
  - Further serum chemistry: urea, serum creatinine, creatinine clearance, total bilirubin, direct bilirubin, LDH, ALT, AST, gamma-glutamyl transferase (gGT), alkaline phosphatase, C-reactive protein, creatinine kinase (CK), CK-myocardial band (MB), TSH
  - Coagulation parameters: Prothrombin time, aPTT and INR
  - Complete blood cell count including white blood cell count (WBC) and differential blood count, hemoglobin (Hb), hematocrit and platelet count
- Adverse events (AEs)
- Serious adverse events (SAEs) and other significant AEs
- Deaths

Statistical methods:

Primary analysis was performed for proportion of patients progression-free after 6 months. The analysis included all patients that received at least one dose of pazopanib and which were assessable with regard to their disease status at 6 months (or before in case of PD prior to 6 months after therapy start; modified intention-to-treat (mITT) population).

PFS (secondary endpoint) and OS were analyzed using the Kaplan-Meier analyses.

Summary - Conclusions:

Efficacy results:

Baseline characteristics:

43 patients treated with pazopanib were evaluable. The median age at start of treatment was 66.0 years. More males (79.1%) than females (20.9%) participated in the study. Patients with clear cell histology and protocol-defined poor-risk factors were included. According to the MSKCC (Memorial Sloan Kettering Cancer Center) prognostic score risk model 67.4% of patients were classified as poor risk at inclusion. Main reason for end of treatment was progression of disease (55.8%).

Primary efficacy: The primary endpoint of the study was to evaluate the proportion of patients free of progression at 6 months (26 weeks ±7 days) after start of first-line therapy with pazopanib. The 6-month PFS rate (exact) was 35.29% (95% CI, 19.7 – 53.5). 34 patients were eligible for analysis.

Secondary efficacy:

Median OS was 9.3 months (95% CI, 6.6 – 22.2).

Median PFS (Kaplan-Meier) was 4.5 months (95% CI, 3.6 – 7.8).

ORR (CR+PR) was 32.4% (95% CI, 17.4 – 50.5).

Median DOR was 9.7 months (95% CI, 1.8 – 12.4).

34 patients were eligible for analysis.

Safety results:

Exposure:

During the study, 43 patients were exposed to pazopanib with median treatment duration of 17.0 weeks (range: 1.6 to 92.0 weeks). The relative mean dose intensity of pazopanib was 98.2% (StD: 6.44%).

Adverse events and NCI-CTCAE toxicities:

40 out of 43 patients in the safety analysis set (SAF) experienced treatment-emergent AEs (TEAEs). A total

Name of Sponsor/Company: iOMEDICO	Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Pazopanib (Votrient®)		
Name of Active Ingredient: Pazopanib		

of 166 TEAEs occurred. The majority of patients presented gastrointestinal disorders (53.5%), general disorders and administration site conditions (32.6%), investigations (27.9%) as well as infections and infestations (20.9%). 88 (53.0%) of the 166 TEAEs were judged to be related to the investigational medicinal product (IMP) pazopanib. 18 TEAEs were graded severe (CTCAE ≥ 3).

28 serious TEAEs (TESAEs) in 19 patients (44.2%) were reported of which five (3.0%) were considered being related to pazopanib.

A total of 27 deaths occurred in this study, including two deaths of unknown cause. 20 deaths were due to tumor progression, 3 due to worsening of comorbidity, one was due to a TESAE (acute renal failure) while patient had documented tumor progression prior to event, and one patient died due to an acute abdomen during follow up. None of the fatal TEAEs was assessed as being related to pazopanib.

Other observations related to safety:

No clinically relevant changes with regard to vital signs and physical findings were observed in this study. Changes in vital signs and clinical conditions were consistent with findings in patients with advanced solid tumors showing moderately to severely impaired general health status.

Due to poor recruitment the FLIPPER trial was prematurely terminated after enrollment of the 60th patient. The target number of 80 enrolled patients could not be achieved.

Conclusion:

FLIPPER demonstrated that pazopanib is effective as first-line treatment for patients with mRCC and mainly poor-risk features. PFS and OS achieved with pazopanib were comparable to those reported with temsirolimus, the only therapy option supported with evidence level 1 in this patient population. Of note, patients appear to respond even better to pazopanib than to temsirolimus.
Taken all data of the FLIPPER trial together, it can be concluded that pazopanib is well tolerated. AE pattern and death rate lie in the expected range. No new or potentially important safety issues were identified during the study. The risk-benefit assessment of pazopanib as first-line treatment in patients with mRCC and mainly poor-risk features is assessed as favorable.

Date of report: 23-Jan-2018