2. Synopsis

Name of sponsor: iOMEDICO AG	Volume: Final v1.0 Pages: 3 – 10	(For National Authority Use Only)
Name of finished product: NA (not applicable)		
Name of active ingredient: Everolimus (Afinitor®)		

Title of study:
An open label, single arm trial to characterize patients with metastatic renal cell carcinoma treated with everolimus after failure of the first VEGF-targeted therapy

Coordinating investigator:
[redacted]

Study centers:
Fifteen centers in Germany enrolled patients in this study (Table 2; section 2.2).

Publication (reference):
NA

Study period:	**Phase of development:**
First-patient-in; date of first enrolment: 21-Mar-2011 Last-patient-in; date of last enrolment: 25-Aug-2015 Last-patient-last-visit; study completion date: 26-Sep-2017	Phase IV

Objectives:

Primary objective

- To assess the rate of patients who were free of disease progression after 6 months of treatment with everolimus as second-line therapy.

Secondary objectives

- To estimate the PFS (progression free survival) of patients having received everolimus as second-line therapy, who had progressed on or after prior VEGF (vascular endothelial growth factor)-targeted first-line therapy
- To assess the OS (overall survival) of patients treated with everolimus as second-line therapy after failure of prior VEGF-targeted first-line therapy.
- To assess the ORR (objective response rate) according to RECIST version 1.1 (Response Evaluation Criteria In Solid Tumors) and the duration of response
- To assess the safety profile of everolimus as second-line therapy after failure of prior VEGF-targeted first-line therapy

Explorative objectives

The exploratory objectives of this study were to investigate the relation between biomarkers and clinical benefit (response, stable disease and progression / no clinical benefit):

- To assess the pre- and post-treatment pattern of circulating markers in serum samples
- To identify protein expression patterns measured in the serum of everolimus-treated patients (second-line therapy), which is predictive of treatment benefit.
- To assess the effect of the pre- and post-treatment pattern of circulating markers with regards to PFS of patients having received everolimus as second-line therapy after failure of prior VEGF-targeted first-line therapy.
- To assess the effect of baseline levels of circulating markers of angiogenesis with regards to PFS of patients treated with everolimus as second-line therapy after failure of prior VEGF-targeted first-line

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therapy.

- To assess the effect of changes of levels of circulating markers of angiogenesis in regard to PFS of patients having received everolimus as second-line treatment after failure of prior VEGF-targeted first-line therapy.
- To assess genomic polymorphisms of the gene encoding FRAP1 (FK506-binding protein 12-rapamycin-associated protein 1), also known as mTOR (mammalian target of rapamycin).
- To assess baseline levels of pVHL (von Hippel Lindau Gene) and pathway activation (e.g. pS6 [phospho-S6-Ribosomal Protein], pAKT [protein kinase B], PTEN [phosphatase and tensin homolog]), in tumor samples when available.
- To assess the mutational status of genes involved in pathway deregulation, e.g. VHL, PI3KCA (phosphoinositide-3-kinase, catalytic, alpha polypeptide), in tumor samples, when available.
- To assess the everolimus trough levels.
- To assess functional MRI (magnetic resonance imaging)-parameters (e. g. DCE [dynamic contrast-enhanced]-MRI, DWI [diffusion weighted imaging] and T1-quantification) at baseline and during everolimus treatment as potential biomarkers (selected study sites only). The report of the MRI-DCE sub-study is stored in the Trial Master File and can be provided upon request .

Please note that the analyses and outcomes of the explorative objectives are not included in this report, but will be performed and published separately by the head of the translational projects. A report is planned for April 2018.

Methodology:
This was an open-label, prospective, multi-center, single arm clinical trial. The clinical trial protocol and its amendments are displayed in Table 1 (section 2.1).

Number of patients (planned and analyzed)	**Planned:** N=80 **Screened:** N=70 Due to a low recruitment rate, recruitment was stopped after enrollment of 70 patients.	**Randomized:** NA **Completed:** N=63	**Analyzed:** <u>Efficacy:</u> FAS (Full Analysis Set): N=63 PP (Per-Protocol) Population: N=49 <u>Safety:</u> SAF (Safety Set): N=63

Diagnosis and main criteria for inclusion:
Patients were included in the study if they aged ≥18 years, were diagnosed with mRCC (metastatic renal cell carcinoma) with or without nephrectomy (partial or total), had at least one measurable lesion at baseline according to RECIST version 1.1, had failed prior VEGFR-TKI (tyrosine kinase inhibitor) first-line therapy for metastatic renal cell carcinoma, had ECOG (Eastern Cooperative Oncology Group) performance status ≤2 and no evidence of CNS (central nervous system) metastases. Patients were ineligible if they had received prior systemic therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus). All inclusion and exclusion criteria are detailed in section 9.3 .

Test product, dose and mode of administration:
Ten mg everolimus (Afinitor®) per os once daily as per current version of SmPC (Summary of Product Characteristics). One cycle consisted of 28 days of continuous administration.

Duration of treatment:
Patients were treated until documented disease progression according to RECIST version 1.1, unacceptable toxicity or discontinuation from treatment for any other reason.

Reference therapy, dose and mode of administration:
NA

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Criteria for evaluation:

Efficacy

Primary endpoint

- Rate of patients who were free of disease progression at 6 months after start of treatment with everolimus as second-line therapy. Disease progression was assessed according to RECIST version 1.1.

Secondary endpoints

- PFS defined as the time interval between start of everolimus treatment (second-line) and documented disease progression or death due to any cause.
- OS defined as the time from date of first intake of everolimus (second-line) to date of death due to any cause.
- Best response, ORR (RECIST version 1.1) and duration of response, defined as time interval between first occurrence of response (partial or complete remission) and disease progression or death (whatever came first)

Safety

- Incidence of AEs (adverse events) and SAEs (serious AEs). Severity grading of AEs was based on NCI (National Cancer Institute)-CTCAE (Common Terminology Criteria for Adverse Events) version 4.02.
- Incidence of laboratory abnormalities (hematology, blood chemistry and urinalysis). Severity grading according to [NCI-CTCAE version 4.02].

Statistical methods

Determination of sample size

Original sample size calculation

If the sample size is73, a two-sided 95% CI (confidence interval) for a single proportion will extend ±10% from the observed proportion for an expected proportion of patients progression-free at six months of 25% using the large sample normal approximation. The total number of 80 enrolled patients initially planned in this trial took into account a drop out rate of approximately 10%.

Due to the low recruitment rate the recruitment was stopped after enrollment of 70 patients. Of these, 63 patients received treatment with everolimus.

Statistical Analysis:

The statistical analysis performed are detailed in the SAP (Statistical Analysis Plan) Version 1.0 dated 04-Feb-2016 (Appendix 16.1.9).

Analysis populations

The statistical analysis comprised the following analysis populations:

Efficacy

- Full Analysis Set: The FAS comprised all enrolled patients having received at least one dose of everolimus. The FAS was the relevant analysis population used in the efficacy evaluation including demographic and other baseline characteristics as well as study treatment evaluations.

- Per Protocol population: The PP population consisted of all patients of the FAS with certain additional criteria:

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- patients without any major protocol deviations (failure of any inclusion / exclusion criteria or no tumor assessment until day 182)
- patients who had completed the minimum exposure requirement of having a relative dose intensity over the first 2 cycles of treatment of at least 50%
- if a patient had progressed, discontinued treatment due to an AE or died before the minimum exposure requirement had been met, that patient was still included in the PP population.

For data where the numbers of patients in the PP population were more than 10% smaller than the number of patients in the FAS, the demographic and other baseline data were also summarized descriptively for the PP population. A supportive analysis of the primary and secondary objectives was also performed on the basis of the PP population.

- Subgroups (FAS/PP):
  - Age: <65 years / ≥65 years
  - Gender
  - BMI at baseline: ≤25 kg/m² / >25 kg/m²
  - ECOG Performance Status at baseline: score 0 / score ≥1

Safety

- Safety Set: The SAF included all patients of the FAS for whom at least one further (post-baseline) information under treatment was available. The SAF was the relevant population used in the safety assessment.

Summary statistics

Summary statistics included the following type of variables:

- nominal and ordinal variables are presented as frequencies and percentages
- continuous variables include number (N) of observations, mean, standard deviation, median, 25th and 75th quartile, minimum and maximum
- corresponding 95% CIs are provided, where applicable

Efficacy Evaluation

Progression Free Survival rate

The 6-month PFS rate was calculated using the Kaplan-Meier method for estimating PFS. Patients without disease progression before the onset of a subsequent anticancer treatment were right-censored at the start date of the subsequent treatment. Patients alive without disease progression and without any subsequent anticancer treatment at the end of observation time were right-censored at the date of last contact. Percentages include 95% CI limits of the 6-months PFS rate presented for FAS and PP and stratified by age at date of informed consent (<65 years / ≥65 years), gender, BMI (body mass index) at baseline (≤25 / >25 kg/m²) and ECOG Performance Status at baseline (0 / ≥1).

Progression Free Survival

PFS was calculated using the Kaplan-Meier method for estimating PFS. Patients without disease progression before the onset of a subsequent anticancer treatment were right-censored at the start date of the subsequent treatment. Patients alive without disease progression and without any subsequent anticancer treatment at the end of observation time were right-censored at the date of last contact. Tables for PFS include data of FAS and of PP and are additionally stratified by age (<65 years / ≥65 years), gender, BMI at baseline (≤25 / >25 kg/m²) and ECOG Performance Status at baseline (0 / ≥1) together with median and quartiles including respective 95% CIs. Frequencies of censored patients are depicted as well.

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Overall Survival
OS was determined using the method of Kaplan-Meier. Patients alive at the end of observation time were right-censored at the date of last contact. Tables for OS include data of FAS and PP and stratified by age (<65 years / ≥65 years), gender, BMI at baseline (≤25 / >25 kg/m²) and ECOG Performance Status at baseline (0 / ≥1) together with median and quartiles including respective 95% CIs. Frequencies of censored patients are depicted as well.

Objective Response Rate
Best response and objective response rate (ORR=CR [Complete Remission] + PR [Partial Remission]) were calculated for FAS and PP population and stratified by age at date of informed consent (<65 years / ≥65 years), gender, BMI at baseline (≤25 / >25 kg/m²) and ECOG Performance Status at baseline (0 / ≥1). Patients without measurable lesions were not included in the different response categories. The frequency and percentage of patients without measurable lesions are presented. Rates are reported with the corresponding 95% CI.

Duration of Response
Duration of response (DoR) was calculated using Kaplan-Meier method. In case no progressive disease (or death) occurred prior to onset of a subsequent treatment, the duration was censored at the onset date of the subsequent therapy. If no subsequent therapy is documented then the duration is censored at date of last contact in case no event (PD, death) occurred. DoR was determined for patients in FAS and PP population for whom any response (CR or PR) was documented. Analysis was stratified by age at date of informed consent (<65 years / ≥65 years), gender, BMI at baseline (≤25 / >25 kg/m²) and ECOG Performance Status at baseline (0 / ≥1). DoR is presented with median and quartiles including respective 95% CIs. Frequencies of events and censored patients are presented as well.

Safety Evaluation

Adverse Events
Summary tables for AEs include the TEAEs (treatment-emergent AEs). An AE was classified as TEAE if it was temporally related to the study medication (AE started or worsened between onset of everolimus treatment and 30 days after end of treatment). Summary tables of the treatment-emergent TEAEs were analyzed in total (SAF) and by groups including sorting by CTCAE severity grade, MedDRA (Medical Dictionary for Regulatory Activities) classified SOC (System Organ Class) and PT (Preferred Term). For the aggregated statistical analyses, an AE was classified as drug-related if the relationship was classified as “related to everolimus” by the investigator.

Clinical Laboratory Evaluations
Laboratory data included clinical chemistry, electrolytes, hematology, and coagulation parameters. Laboratory parameters were solely analyzed based on the quantitatively documented parameter values including respective CTCAE severity grade. CTCAE severity grades at baseline and shift tables (baseline to worst on-treatment) are presented.

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Summary – Overall Conclusion:

A total of 63 pts were enrolled between 03/2011 and 08/2015. Median age was 65 years. Majority of patients were male (76.2%), ECOG 0-1 (96.8%), and were secondary refractory to first-line VEGFR-targeted therapy (63.5%). Pts received treatment for a median of 3.7 months with median relative dose intensity of 100%.

Efficacy results

Primary Endpoint

- 6-Months PFS Rate

	FAS (N=63)	PP (N=49)
6-Months PFS Rate [95%-CI]	39.3% (27.0% - 51.3%)	44.6% (30.0% - 58.2%)

6-Months PFS rate as assessed in pre-specified subgroups (FAS) was 54.4% (age ≥65 years, N=32) vs. 23.7% (age < 65 years, N=31), 51.4% (BMI >25kg/m², N=41) vs. 18.2% (BMI ≤25kg/m², N=22), 41.6% (ECOG 0, N=36) vs. 37.0% (ECOG 1-2, N=27), and 29.3% (female, N=15) vs. 42.2% (male, N=48).

Secondary Endpoints
(Analysis population: FAS, n =63)

- Median PFS (95% CI): 3.8 months (3.2 - 6.2)
- Median OS (95% CI): 16.8 months (14.3 - 24.3)
- ORR (CR+PR): 7.9% (n=5)
  - CR: n=0 (0%)
  - PR: n=5 (7.9%)
- DoR (95% CI): 12.5 months (6.7 – 31.2)

Safety results
(Analysis population: SAF, n=63)

Extent of exposure

At maximum, 38 cycles of treatment with everolimus were observed during the course of the study. The median initial dose of everolimus was 10 mg once daily in each of these 38 cycles. The median duration of therapy with everolimus was 3.7 months (range: 0.7–34.7 months). The majority of the patients received 2 (n=12; 19.0%), 3 (n=10; 15.9%) or 4 (n=9; 14.3%) cycles of treatment. The median relative dose intensity of everolimus was 100% (range: 47.1–100).

Therapy modifications

The most frequently reported therapy modification was interruption of treatment (41.3%; n=26) followed by dose reduction (22.2%; n=14), cycle missed (19.0%; n=12) and delay of cycle (1.6%; n=1).

Discontinuation of study treatment

All 63 patients enrolled had discontinued study treatment at time of study termination. The most frequently

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reported reason for end of everolimus treatment was progressive disease (73.0%; n=46). There were 7 (11.1%) patients reported with TEAEs and discontinuation of everolimus treatment (11 cases in total; 9 cases attributable to everolimus).

Treatment-emergent adverse events NCI-CTCAE toxicities

Treatment-emergent adverse events

A total of 61 (96.8%) patients were reported with TEAEs (any event) during the course of this study, of these, 36 (57.1%) patients experienced TEAEs grade 3/4 (69 cases in total). On the SOC level, the most frequently (>5% of patients) reported TEAEs grade 3/4 were “blood and lymphatic system disorders” (19.0%; n=12), “metabolism and nutrition disorders” (14.3%, n=9), “general disorders and administration site conditions” (11.1%; n=7), “infections and infestations” (11.1%, n=7), “gastrointestinal disorders” (9.5%; n=6), “investigations” (7.9%; n=5), and “respiratory, thoracic and mediastinal disorders” (6.3%; n=4).

Forty-nine (77.8%) patients were reported with treatment-emergent everolimus-related AEs. Twenty-four (38.1%) patients were reported with a TEAE grade 3/4 assessed as related to everolimus (39 cases in total).

Serious treatment-emergent adverse events

Thirty-one (49.2%) patients experienced a treatment-emergent SAE during the course of the study. Nineteen (30.2%) patients were reported with a SAE grade 3/4 (27 occurrences), of these, the most frequently (>5% of patients) reported SOCs were “infections and infestations” (7.9%; n=5) and “respiratory, thoracic and mediastinal disorders” (6.3%; n=4).

Twelve (19.0%) patients were reported with treatment-emergent SAEs attributable to everolimus. Nine (14.3%) patients were reported with treatment-emergent SAEs grade 3/4 attributable to everolimus (11 cases in total). The most frequently (>2% of patients) reported SOCs were “respiratory, thoracic and mediastinal disorders” (4.8%; n=3) and “infections and infestations” (4.8%; n=3).

Fatal treatment-emergent adverse events

Five (7.9%) patients were reported with a fatal (grade 5) serious TEAE during the course of the study. The 5 fatal TEAEs were malignant neoplasm progression (n=3), metastases to central nervous system (n=1) and upper gastrointestinal hemorrhage (attributable to everolimus; n=1).

Deaths

In total, 45 (71.4%) patients died during the course of study. The majority of the patients (n=41; 65.1%) were reported having died due to tumor disease (progression). The cause of death for one (1.6%) patient was an everolimus-related SAE (i.e. upper gastrointestinal hemorrhage).

Other observations related to safety – laboratory tests

One patient was reported with 9 serious TEAEs in total, of these, 5 cases were laboratory abnormalities reported as serious TEAE (none of them were attributable to everolimus). Some of these fell into the group of parameters of interest; the MedDRA PTs were alanine aminotransferase increased (n=1) and Gamma-glutamyltransferase increased (n=2). These laboratory abnormalities were most likely associated with the other serious TEAEs reported for this particular patient (stomatitis [related], edema peripheral [not related], cardiac failure congestive [related], and pneumonia [related]).
Two other patients were reported with a serious, everolimus-related grade 3 anemia and a serious non-related grade 3 anemia, respectively.

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Overall conclusion

This phase IV study was performed in compliance with the ICH GCP guidelines and comprised 63 mRCC patients having received everolimus as second-line therapy following failure of prior VEGF-targeted first-line therapy.

Efficacy and safety profile are in line with results from other clinical trials with everolimus and compatible to the current SmPC. However, differences were noted for 6-month PFS rate in pre-specified subgroups.

No new or potentially critical safety issue was identified in this study.

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