PROTOCOL

Itraconazole (ITRA) with standard radiotherapy (RT) and temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM)
ITRA-RAD: Phase I Clinical Study

„ITRA-RAD“

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Sponsor-Code:	IIT-2024/01		
Phase of the clinical trial:	I	Participating Trial Sites:	1

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RELEASE OF THE PROTOCOL

Sponsor-Code: IIT-2024/01

Version and Date of the protocol: 01/23.10.2024

The undersigned declare

• that they have completely read and understood this protocol and undertake to carry out the clinical trial (CT) in accordance with this protocol,

• that they undertake the CT in accordance with the Clinical Trial Regulation) CTR, the national Medicines Act (AMG), the principles of the Declaration of Helsinki, the principles of Good Clinical Practice (ICH E6 (R2)), the sponsor's quality management system and the requirements of the supervisory authorities regarding the original data comparison to carry out,

• that they undertake to use the investigational medicinal product (IMP) exclusively in accordance with the specifications of the protocol.

We note that changes to the protocol may only be made in the form of written amendments/modifications and any deviation from the protocol may lead to the premature termination of the CT.

	Date	Signature
Sponsor Prof. Dr. rer. nat. Daniela Dieterich	_____	_____
Statistican Dipl.-Math. Anke Lux	_____	_____
Principal Investigator Dr. med. Dusan Milanovic	_____	_____

DECLARATION OF ACCEPTANCE OF THE PROTOCOL

Sponsor-Code: IIT-2024/01

Version and Date of the Protocol: V01/23.10.2024

The undersigned declare

• that they committed themselves to the CT in accordance with the CTR, the AMG, the principles of the Declaration of Helsinki, in accordance with the principles of Good Clinical Practice (ICH E6 (R2)) and the requirements of the supervisory authorities regarding the original data comparison and to carry out the auditing/inspection of the audit,

• that they undertake to use the IMP in accordance with the specifications of the protocol,

• that they have read and understood this protocol completely and undertake to carry out the CT in accordance with this protocol,

• that, if necessary, all members of the trial team are informed by the principal investigator about modifications and trained accordingly.

We note that changes to the protocol may only be made in the form of written amendments/modifications and any deviation from the protocol may lead to the premature termination of the CT.

	Date	Signature
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Table of Content / *Inhaltsverzeichnis*

1 Introduction / *Einleitung*

1.1 German Synopsis / *Deutsche Synopse*

Titel	Itraconazol (ITRA) mit Standard-Strahlentherapie (RT) und Temozolomid (TMZ) bei Patienten mit neu diagnostiziertem Glioblastom: eine Phase 1 Studie
Kurztitel der KP	ITRA-RAD
Studientyp	Nicht-kommerzielle klinische Prüfung (IIT) mit Arzneimitteln
Studiendesign	Phase I monozentrische, Dosis-Eskalation Studie
Zielpopulation/Indikation	Patienten mit erstdiagnostiziertem Glioblastom
Studienziele	<u>Primäre Endpunkte:</u> • Bestimmung der maximal tolerierten Dosis (MTD) von ITRA, das gleichzeitig mit der Standardbehandlung (RT und TMZ) verabreicht wird <u>Sekundäre Endpunkte:</u> • Bestimmung des Sicherheitsprofils von ITRA gemäß der Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 des National Cancer Institute (NCI). • Bestimmung der Wirkung von ITRA auf das Gesamtüberleben (OS) • Beurteilung der Verträglichkeit des Behandlungsschemas um die von Patienten berichteten gesundheitsbezogenen Ergebnisse zur Lebensqualität zu bewerten
Einschlusskriterien	1. Histologisch bestätigte Diagnose von GBM 2. Keine vorherige Behandlung außer einer Operation (d.h. keine vorherige RT, lokale Chemotherapie oder systemische Therapie) ist zulässig. Die Patienten müssen in der Lage sein, sich seriellen MRT-Untersuchungen zu unterziehen (Computertomographie ersetzt möglicherweise nicht die MRT) 3. Patienten, die für eine Operation nicht in Frage kamen und nur eine Biopsie hatten und mit Standard-RT (60 Gy in 30 Fraktionen) und TMZ behandelt werden konnten 4. ≥ 18 Jahre alt 5. Ausreichende Nieren- und Leberfunktion sowie hämatopoetische Kapazität 6. ECOG-Leistungsstatus ≤ 2 und Sie müssen in der Lage sein, ganze Kapseln zu schlucken 7. Muss in der Lage sein, die Protokollanforderungen zu verstehen und einzuhalten und die Einverständniserklärung unterschrieben haben

Ausschlusskriterien	1. Vorherige Behandlung mit systemischer Chemotherapie oder RT oder einer anderen Art von Prüfpräparat zur Behandlung von Hirntumoren 2. Nachweis einer akuten intrakraniellen oder intratumoralen Blutung > Grad 1 durch MRT oder Computertomographie. An der Studie können Patienten mit sich auflösenden Blutungsveränderungen, punktuellen Blutungen oder Hämosiderin teilnehmen 3. Schwangere oder stillende Frau 4. Herzinsuffizienz (kompensierte oder dekompensierte) 5. Schwere Lebererkrankung wie Leberzirrhose, akute oder chronische Hepatitis 6. Andere schwerwiegende Erkrankungen wie erhebliche Herzrhythmusstörungen, schweres Atemversagen oder akutes Nierenversagen 7. Andere bösartige Erkrankungen außer chirurgisch entferntem Nicht-Melanom-Hautkrebs oder Carcinoma in situ des Gebärmutterhalses oder behandeltem Prostatakrebs im Frühstadium 8. Zuvor festgestellte Allergie oder bekannte Überempfindlichkeit gegen Bestandteile von ITRA oder TMZ 9. Eine aktuelle Behandlung mit ITRA

Methodik/ Ablauf/ Zeitplan	**Visite 1**
	• **Patienteninformation**
	• **Einwilligungserklärung**
	  • Ein-und Ausschlusskriterien
	  • spezifische Krankengeschichte inkl. aktueller Medikation
	  • Körperliche Untersuchung
	  • Durchführung eines EKG
	  • Blutentnahme zur allgemeinen Gesundheitsbeurteilung:
	AST, ALT, Bilirubin, Natrium, Kalium, Hämoglobin, kleines Blutbild inkl. Leuko-, Neutro-, Lympho-, Thrombo- und Erythrozyten und ACTH, aber nur wenn die Teilnehmer von Beginn der KP an Prednisolon nehmen müssen
	  • BMI
	  • HRQoL - EORTC Quality of Life Questionnaire (QLQ)-C30 und Brain Cancer Module (BN20)
	
	Visit 2 (innerhalb von 7 Tagen nach V1)
	  • Planung der Strahlentherapie +TMZ (Standardtherapie)
	  • ITRA Ausgabe und Beginn der Einnahme

<table>
<tr><td></td><td colspan="3">
Abfrage AE und SAE
Visit 3 (innerhalb von 5 Tagen nach V2):
Beginn der Standardtherapie
Abfrage AE und SAE
Visit 4 (7 Tagen nach V3 +/- 1 Tag):
Blutentnahme zur allgemeinen Gesundheitsbeurteilung siehe V1
Abfrage AE und SAE
Visits 5 – 7 wöchentlich (+/- 1 Tag):
Blutentnahme zur allgemeinen Gesundheitsbeurteilung siehe V1
Abfrage AE und SAE
Visit 8 (7 Tagen nach V7 +/- 1 Tag)
Körperliche Untersuchung
Blutentnahme zur allgemeinen Gesundheitsbeurteilung siehe V1
BMI
Abfrage AE und SAE
Visit 9 (7 Tagen nach V8 +/- 1 Tag):
Ende der Standardbehandlung + ITRA
Rückgabe der leeren und/oder verbleibenden Blisterpackungen
Blutentnahme zur allgemeinen Gesundheitsbeurteilung siehe V1
Durchführung eines EKG
HRQoL - EORTC Quality of Life Questionnaire (QLQ)-C30 und Brain Cancer Module (BN20)
Abfrage AE und SAE
Allgemein: ACTH- Bestimmung unabhängig von der Visite nur wenn die Teilnehmer während der Behandlung Symptome eines erhöhten Hirndrucks entwickeln und eine Behandlung mit Prednisolon erforderlich ist, dann bei der darauffolgenden Visite
</td></tr>
<tr><td>Anzahl Prüfzentren</td><td>1</td><td>Anzahl teilnehmende Länder</td><td>1</td></tr>
<tr><td>Patientengesamtanzahl</td><td>9-15</td><td>Patientenzahl je Prüfzentrum</td><td>9-15</td></tr>
<tr><td rowspan="2">Geplante Studieneck-Zeitdaten</td><td>Erster Patient, erste Behandlung (FPFV)</td><td colspan="2">Q4/2024</td></tr>
<tr><td>Letzter Patient, letzte Behandlung (LPLV)</td><td colspan="2">Q4/2025</td></tr>
<tr><td>Studiendauer pro Patient</td><td colspan="3">7 Wochen</td></tr>
<tr><td>Prüfungsbezogene Verfahren und Laboruntersuchungen</td><td colspan="3">1 zusätzliche Laboruntersuchung zur Routine an V9</td></tr>
</table>

Statistische Auswertung	Primär soll die maximal tolerierte Dosis (MTD) ermittelt werden, verbunden mit der Angabe aller Nebenwirkungen und Toxizitäten. Die Wirkung am Tumor (Response), die Verträglichkeit sowie die Lebensqualität werden sekundär betrachtet. Sämtliche diesbezügliche Angaben erfolgen in erster Linie deskriptiv.

List of responsible persons / *Liste der verantwortlichen Personen*

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List of Abbrevations / Abkürzungsverzeichnis

Abbrevation	Description
AE	Adverse Event
ADR	Adverse Drug Reaction
1.2 PAM	PI3K/AKT/mTOR
AMG	Arzneimittelgesetz
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASR	Annual Safety Report
ASTRO	American Society Therapeutic Radiation Oncology
BSA	Body Surface Area
CBC	Complete Blood Count
CNS	Central Nervous System
COV	Close-out-Visit
CSF	Cerebrospinal Fluid
CRF	Case Report Form
CRT	Chemoradiotherapy
CT	Clinical Trial
CTCAE	Common Terminology Criteria of Adverse Events
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation (EU) No 536/2014
Dhh	Desert Hedgehog
DLT	Dose LimitingToxicity
DRKS	German Clinical Trial Register (Deutsches Register für klinische Studien)
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Elektrocardiogramm
ESTRO	European Society Therapeutic Radiation Oncology
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GBM	Glioblastoma
GCP	Good Clinical Practice
GIC	Glioma Initiating Cells
GLI	Glioma Associated Oncogene
GTV	Gross Tumour Volume
Gy	Gray
Hh	Hedgehog Pathway
HRQoL	Health-Related Quality of Life
ICH	International Council for Harmonization
IIT	Investigator Initiiated Trial

ITRA	Itraconazole
IMP	Investigational Medicinal Product
ISF	Investigator Site File
KKS	Koordinierungszentrum für Klinische Studien
KP	Klinische Prüfung
LPLV	Last Patient Last Visit
MDT	Multidisciplinary Team
MGMT	O^6-methylguanine–DNA methyltransferase
MRI	Magnetic Resonance Imaging
MV	Mega Voltage
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PM	Project Manager
PPI	Proton-pump inhibitor
RT	Radiotherapy
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SESAR	Suspected Expected Serious Adverse Reaction
Shh	Sonic Hedgehog
SMO	Smoothened
SmPC	Summary of Product Characterization
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMZ	Temolozomide
VEGF/VEGFR-2	Vascular endothelial growth factor/Vascular endothelial growth factor receptor 2

Necessity to conduct the clinical trial / *Notwendigkeit der Durchführung der klinischen Prüfung*

Rationale

2 Glioblastoma (GBM) is the most common brain tumour of astrocytic origin. [**1**]. Due to its highly infiltrative growth and difficult differentiation between tumour and the surrounding oedematous brain, microscopic resection is virtually impossible. The standard therapeutic strategy includes surgery and concurrent
2.1 chemo radiotherapy (CRT) with Temozolomide (TMZ) followed by treatment with maintenance TMZ [**2**] without or with Tumor-Treating Fields [**3**]**.** Despite the dramatic advances in the understanding of GBM molecular biology [**4**] and development of new-targeted therapies [**5, 6, 7**] a positive influence on the survival of these patients has not yet been observed. Following recent reports from international meetings such American Society of Clinical Oncology (ASCO), ASTRO (American Society for Radiation Oncology) and The European Society for Radiotherapy and Oncology (ESTRO) it appears that overall survival (OS) is unlikely to improve what is currently seen with standard of care therapy. The prognosis of patients with this incurable, aggressive and recurrent neoplastic disease remains poor with a best reported median survival time of around 20 months [**3**] indicating the urgent need for new therapeutic approaches.

Modern anti-cancer pharmaceutical drugs (targeted agents and immunotherapies) are expensive, and several are not associated with substantial improvements in patient outcomes such as survival. Whilst there is major ongoing research into developing new effective agents, there has been significant interest in taking simple, off-patent therapies for treating other disorders and using their anti-cancer properties as potential effective therapies when added to standard systemic treatments.

In this study we aim to repurpose Itraconazole (ITRA) (a common antifungal) and administer it with standard therapy (surgery followed by TMZ and RT) with the aim to determine maximum tolerated dose (MDT) of ITRA given concurrently with TMZ and RT in patients with GBM.

2.2

Hh signaling pathway / *Hh Signalwege*

The Hedgehog (Hh) signalling pathway has a crucial role in normal embryonic development. The Hh family comprises three extracellular ligands - sonic hedgehog (Shh), Indian hedgehog (Ihh), and desert hedgehog (Dhh). The other important members of this pathway are a transmembrane receptor and a transmembrane protein called Smoothened (SMO) and glioma-associated (GLI) transcriptional factors which are effectors of this pathway [**8**]. In most normal adult tissues, this pathway is silenced but aberrant Hh signaling has been detected in many human cancers, including GBM [**9**] implicating an important role in the initiation of carcinogenesis and subsequent tumour growth. It has been shown that SMO is highly expressed in high-grade gliomas compared with low-grade gliomas and normal brain tissues [**10**]. Glioma stem cells are alternatively called glioma initiating cells (GIC) and Shh signaling plays an essential role in their self-renewal and capacity for initiation of tumour growth in orthotopic models [**11**]. In different *in vitro* and *in vivo* models it has been demonstrated that inhibition of Hh caused significant antiglioma activity [**12, 13**].

Vismodegib (GDC-0449) is an oral inhibitor of SMO which is approved for the treatment of localy advanced or metastatic basal cell carcinoma of the skin [**14**].

In one a two-arm, multicenter phase 0/II study treatment with this drug was well tolerated, reached tumor, and inhibited $CD133^+$ neurosphere formation, but had little clinical efficacy as a single agent in patients with recurrent GBM (rGBM) as a sole agent [**15**]. These authors concluded that growth and maintenance of rGBM is not solely dependent on the SHH pathway thus targeting SMO may require combined approaches.

Hh pathway also protects glioma cells against ionising irradiation and its inhibition reverses this protection [**16**]. Also, this pathway can be activated by CRT [**17**] thereby potentially limiting its efficacy. Hh signaling is involved in the regulation of MGMT expression and chemoresistance to TMZ. Inhibition of this pathway has been shown to result in decreased MGMT expression and increased sensitivity to TMZ treatment [**18**].

Due to the fact that the Hh pathway not only plays a role in the progression of GBM, but can also contribute to resistance to standard therapy, it is anticipated that ITRA in combination with standard treatment will increase sensitivity towards standard RT + TMZ and therefore demonstrate therapeutic benefit in patients with GBM.

Unlike GDC-0449 which specifically inhibits SMO, ITRA, in addition to affecting SMO, on the other hand inhibits multiple targets such PI3K/AKT/mTOR (PAM) signalling pathway or Vascular endothelial growth factor/Vascular endothelial growth factor receptor 2 (VEGF/VEGFR-2) [**19**] that play an important role in GBM progression and angiogenesis.

2.3 ITRA and Hh signalling – evidence of anti-tumour activity from preclinical studies / *ITRA- und Hh-Signalisierung – Hinweise auf Antitumoraktivität aus präklinischen Studien*

Kim et al. screened a library of ~2400 FDA-approved or post-phase I drugs for activity in inhibition of Hh signaling [**20**]. They found ITRA, a systemic antifungal, to be a potent antagonist of the Hh signaling pathway. Mechanistically, ITRA inhibits SMO and prevents the ciliary accumulation of SMO normally caused by Hh stimulation. In the U87 orthotopic GBM model, treatment with ITRA caused significant growth suppression [**21**]. Angiogenesis is a key characteristic of this tumour **[22]**; VEGFR2 is an important mediator of this process and was inhibited by ITRA **[23]**. ITRA also caused dose-dependent inhibition of VEGF- and basic fibroblast growth factor mediated angiogenic stimulation when measured in terms of endothelial cell proliferation, migration, and tube formation. These results were confirmed using primary xenograft models of human non-small cell lung cancer **[24]**.

2.4 ITRA in clinical studies/trials / *ITRA in klinischen Studien/Prüfungen*

Although ITRA has not yet been used in GBM it has shown activity as a single agent/when used synergistically in other cancers as described in detail below, with promising results.

In one clinical study, patients with locally advanced Basal Cell Carcinoma of the Skin were treated with ITRA as the sole agent (100 mg twice daily or 200 mg twice daily) **[25]**. The average tumour size was reduced by 24% and GLI1 expression by 65%. 2/33 patients discounted treatment due to side effects; one due to grade 2 fatigue and one due to grade 4 heart failure (possibly linked to previous lymphoma treatment). ITRA was well tolerated with no other grade 3 or 4 side effects reported.

In another clinical study, patients with relapsed metastatic non-small lung cancer (NSCLC) were treated with Pemetrexed and 200 mg/day ITRA or Pemetrexed and Placebo **[26]**. Patients who were treated with Pemetrexed and ITRA had significantly improved OS compared to patients treated with Pemetrexed alone (30 vs. 8 months, p=0.021). Treatment was well tolerated and no differences in the side effects between these two groups were reported.

In another clinical study, patients with NSCLC who were planned for surgical resection were treated with ITRA 300 mg orally twice daily for 10-14 days [**27**]. It has been reported that treatment with ITRA caused concentration-dependent early antivascular, metabolic, and antitumor effects in these patients.

A phase II randomised trial in men with castration resistant prostate cancer patients were treated with single agent ITRA (200 mg/day or 600 mg/day) **[28]**. Better tumour responses were documented in group of patients who were treated with 600 mg/day but adverse events were generally more common in the high-dose than in the low-dose arm. Grade 3 adverse events in the low-dose arm included fatigue (5.9%), anorexia (5.9%), and rash (5.9%). The most frequent Grade 3 toxicities in the high-dose arm were hypokalemia (10.3%), hypertension (6.9%), and rash (3.4%). No grade 4 toxicities were observed. 5.9% of patients in the low-dose arm and 13.8% in the high-dose arm came off study as a result of toxicities. It was reported at the American Society of Clinical Oncology (June 2019, Chicago) that the addition of 400 mg ITRA to chemotherapy with S1, Oxaliplatin, nab-Paclitaxel demonstrated excellent efficacy (high conversion surgery rate) and acceptable toxicities in patients with unresectable advanced or recurrent gastric cancer **[29]**. From 23 patients enrolled in this study, the median OS was 22 months and 1-year OS rate was 81.8%. Grade 3/4 neutropenia was reported in 5 (22%) patients and grade 2 peripheral sensoryneuropathy in 6 (26%). No grade 3 or4 thorombocytopenia was reported. Notably all of these side effects can be related directly to treatment with chemotherapy.

It has been shown that treatment with 200 mg ITRA once daily significantly decreased the severe epistaxis and improved quality of life in patients with hereditary haemorrhagic teleangiectasia **[30].** In this condition, levels of VEGF are elevated and inhibition of VEGF caused decrease of bleeding.

2.5 Cerebrospinal pharmacokinetics and brain concentration of ITRA / *Zerebrospinale Pharmakokinetik und Gehirnkonzentration von ITRA*

Although not administered previously to patients with GBM it is anticipated that ITRA will cross the blood brain barrier because it has demonstrated anti-fungal activity against brain infections **[31-33]** (meningitis, abscess). Based on the properties of ITRA (being a poorly water soluble drug) and cerebrospinal fluid (CSF) being an aqueous solution significant amounts of ITRA would not be predicted to be detected in CSF. However, ITRA is highly lipophilic and therefore has been detected in many organs and tissues (skin, lung, kidney, liver, fat, spleen, muscle and bone) at a higher concentration than that seen in plasma (by a factor of 1.5–20) **[34].** Lipophilicity is also one of the most important drug characteristics related to its optimal penetration into the CNS **[35]**. It has been shown that one hour after a single intravenous dose of ITRA, concentrations in the brains of healthy rats exceeded plasma concentrations by a factor of 1.7 and after 24 hours concentrations were 24 times higher **[36]**.

In human subjects, no Phase 0 studies have been conducted to detect concentrations of ITRA in brains. Despite this and based on favourable ITRA physicochemical properties (lipophilic agent), ITRA demonstrates good activity in the treatment of CNS fungal infections. Excellent results have been reported

in the treatment of Cryptococal Meningitis **[31]**, CNS histoplasmosis **[33]** and Aspergillus brain abscesses **[32]**. Furthermore, the table (appended) indicates that although CSF penetration of ITRA is <1% the brain tissue penetration is 50≥100%.

Finally, RT may increase permeability of Blood Brain Barrier which may lead to additional penetration of ITRA into GBM tissue **[37].**

Preclinical results / *Die präklinischen Ergebnisse*

Pre-clinical studies undertaken by our group indicate that ITRA will have a synergistic effect when used in combination with TMZ and RT in GBM **[38]**. The effects of treatment with ITRA, TMZ and RT (single agents or in different combinations) has been tested in established U251, U343 and primary GIN28, GIN31 GBM cell lines and GIN28 and GIN31 3-D Tumour spheroid models. Measured by Colony Forming and Alamar Blue Assays, treatment with ITRA (2 and 5 µM) as a sole agent caused antiproliferative effects in U251 and U343 cells. ITRA significantly increased the radiosensitivity of both cell lines in cases where the cells were irradiated with a clinical relevant dose (2 Gy). ITRA did not enhance the effects of TMZ in U251 cells but in U343 cells additive effects were observed. In both cell lines, the strongest effects were observed when ITRA+TMZ+RT were given in combination (synergistic/additive). In primary cell lines, GIN28 and GIN31, treatment with TMZ (50-400 µM) had a modest effect on the cell viability while the treatment with ITRA (2-20 µM) had more pronounced effects on cell viability. If these cells were treated with combination of TMZ and ITRA no additional antiproliferative effects were observed compared to ITRA alone In GIN31 spheroids, treatment with TMZ (even at the highest tested concentration) did not have any influence on the spheroid diameter while treatment with 20 µM ITRA reduced spheroid diameter by 37%.

Finally, results from Comet studies using U251 cells showed that a combination of ITRA and 5 Gy irradiation clearly enhanced immediate comet formation while ITRA treatment alone did not produce any detectable DNA damage **[35]**.

2.6

2.7

Hypothesis / *Hypothese*

The Hh pathway plays an important role in the development and progression of GBM. We propose that patients with GBM who are treated with RT+TMZ would benefit from simultaneous treatment with ITRA that inhibits multiple important targets involved in development of treatment resistance and progression (Hh, PAM) of this disease. It is anticipated that all patients (those with methylated/unmethylated MGMT) will benefit from our treatment strategy.

ITRA is an oral, well tolerated antifungal drug that has no significant influence on TMZ metabolism and which has a toxicity profile that does not overlap with TMZ or RT. ITRA is widely available, and comes with a track record of improving outcomes of cancer patients through the inhibition of the Hh signalling pathway and through inhibition of other relevant events responsible for GBM progression mentioned above.

Prüfpopulation / *Trial Population*

Inclusion criteria / *Einschlusskriterien*

1. Histologically confirmed diagnosis of GBM
2. No previous treatment except surgery (ie, no previous RT, local chemotherapy, or systemic therapy) is allowed. Subjects must be able to undergo serial MRIs (computerized tomography may not substitute for MRI])

3

3.1

3. Patients who were not candidates for surgery and had biopsy only and could be treated with standard RT and TMZ
4. ≥ 18 years old
5. Adequate renal and hepatic function and hematopoietic capacity
6. ECOG performance status of ≤ 2 and must be able to swallow whole capsules
7. Must be able to understand and comply with the protocol requirements and has signed the informed consent document

Exclusion criteria / *Ausschlusskriterien*

3.2

1. Previous treatment with systemic chemotherapy or RT or any other type of investigational agent for the treatment of brain tumours
2. Evidence of acute intracranial or intratumoural haemorrhage > Grade 1 either by MRI or Computertomography scan. Subjects with resolving haemorrhage changes, punctate haemorrhage, or hemosiderin may enter the study
3. Pregnant or breastfeeding woman
4. Congestive heart failure (compensate or decompensate)
5. Serious liver disease such a cirrhosis, acute or chronic hepatitis
6. Other serious illness such as significant cardiac arrhythmias, severe respiratory failure or acute kidney failure
7. Other diagnosis of malignancy excepting surgically excised non-melanoma skin cancer or carcinoma in situ of the cervix or treated early stage prostate cancer
8. Previously-identified allergy or hypersensitivity to components of either the ITRA or TMZ formulations

3.3

9. Current treatment with ITRA for fungal infection

3.4

Number of Participants / *Teilnehmerzahl*

We plan to apply the classical 3+3 design in order to determine the MTD of ITRA (9 -15 patients).

Recruitment / *Rekrutierung*

Potential study participants will be identified as part of the multidisciplinary tumor conference (MDT) at the UKMD and Städtisches Klinikum Olvenstedt Magdeburg. The patients are made aware of the trial in the respective clinics where the operation will be conduct and are provided with the patient information. Therefore there is enough time to make a decision about the possible study participation. At their first presentation to the Department of Radiation Therapy for consideration of adjuvant treatment they will be

screened, recruited and consented for this trial. This process will be performed according to the submitted Recruitment and Informed Consent Template (EudraLex Vol. 10, see Chapter 10.3).

3.5 Contraception during the trial / *Verhütung während der Studie*

Prior to the commencement of the trial, all female participants must undergo a pregnancy test. However, it should be noted that pregnancy tests can only reliably confirm pregnancy a few days post-conception. Women who are unable to conceive are exempt from this requirement. For participants under the age of 50, information regarding the date of their last menstrual period will be requested.

Participants are required to consistently prevent pregnancy throughout the duration of the study, as itraconazole poses a risk to the developing fetus. Moreover, it is critical to ensure that the investigational drug is not transmitted to the participant's partner. To mitigate this risk, patients are advised to use condoms during sexual intercourse for the duration of the study.

Women who are unable to conceive—whether due to hysterectomy, oophorectomy, tubal removal or blockage, menopause, or sexual relations exclusively with partners who do not produce sperm—must nonetheless utilize condoms to prevent the transmission of the medication. Fertile women, capable of conception, are encouraged to consider additional contraceptive measures, including:

- Barrier methods with localized effects on the endometrium, such as levonorgestrel-releasing intrauterine systems (IUS) or copper-releasing intrauterine devices (IUD).
- Behavioral methods, such as sexual abstinence.
- Double-barrier methods, such as the use of male condoms in combination with an additional barrier method.
- Surgical methods, including partner vasectomy (in cases where the partner is the only sexual partner) or tubal ligation/removal.
- Single barrier methods, including male or female condoms with or without spermicide, or cervical caps, diaphragms, or sponges with spermicide.

Itraconazole may elevate the concentrations of estrogens and progestins, which can result in adverse effects (e.g. abnormal bleeding) and diminish the efficacy of contraceptive methods. Therefore, the use of systemic hormonal contraceptives containing progestins and/or estrogens—such as implants, oral contraceptives, injections, transdermal patches, or "mini-pills"—is not recommended during the trial. Patients are advised to seek guidance from the gynecology department if necessary.

Participants must commence contraceptive use at least two weeks prior to the start of the trial to ensure they are not pregnant at the onset of the study. Contraception must be diligently maintained throughout the trial and is advised for an additional two months following its completion.

3.6 Exclusion of participants / *Ausschluss von Teilnehmern*

1. Participants can withdraw from the CT or withdraw/withdraw their consent at any time without giving reasons.

2. Participants may also be excluded by the principal investigator/investigator for reasons of health risk or non-compliance in the conduct of the CT.

The reason for exclusion from the CT must be documented in the source data (study file) and in the Case Report Form (CRF).

Benefit-Risk-Assessment / *Nutzen-Risiko-Abschätzung*

Due to interactions with multiple targets involved in GBM progression, well known toxic profile, gut tolerability and no overlapping toxicity with standard treatment (RT+TMZ) we suggest that the potential benefits of ITRA treatment will outweigh the potential risks.

3.5 ITRA was patented in 1978 and approved for medical use by the FDA in 1992. It is on the WHO Model List of Essential Medicines.

Investigational Medicinal Product / *Prüfmedikation*

Investigational Medicinal Product / *Prüfmedikation*

4

Itraconazol Aristo 100 mg Hartkapseln (Itraconazole 100 mg per capsule) – for details please see
4.1 SmPC from 06/2023.

Aristo Pharma GmbH
Wallenroder Straße 8-10
13435 Berlin

Email: info@aristo-pharma.de

4.2 ### Packaging and labeling of the IMP / *Verpackung und Kennzeichnung des Prüfpräparates*

The IMP will be supplied by the pharmacy via direct purchase from the above mentioned Pharmaceutical Manufacturer.

IMP is an authorised product and is labelled in accordance with Title V of Directive 2001/83/EC. There
4.3 are no specific circumstances regarding the conduct of the CT which require additional labelling.

Dosage and Method of Administration / *Dosierung und Art der Anwendung*

IMP	Dosage form	Dosage	Method of Administration
Itraconazole	Capsule	100 mg	oral

Three ITRA doses will be considered: 2 x 100 mg ITRA daily, 2 x 200 mg ITRA daily and 2 x 300 mg ITRA. The starting dose will be 2 x 100 mg ITRA daily.

We plan to apply the classical 3+3 design in order to determine the maximum tolerated dose (MTD).

According to this approach, the following scenarios are possible:

First cohort - 2 x 100mg ITRA

a) **Three patients** will receive the starting dose of 2 x 100mg ITRA if no dose-limiting toxicity (DLT) occurs move to the next level of 2 x 200 mg ITRA

or

b) Three patients will receive the initial dose of 2 x 100mg ITRA if one DTL occurs the cohort will expanded to six patients. If no further DTL occurs in the additional patients the dose will be expanded to 2 x 200mg ITRA. If one or more DTL occurs the MTD is reached.

or

c) Three patients will receive the initial dose of 2 x 100mg ITRA if two or more dose-limiting toxicity occurs the cohort will expanded to six patients the MTD is reached.

Second cohort - 2 x 200mg ITRA

d) **Three patients** will receive the initial dose of 2 x 200mg ITRA only if no dose-limiting toxicity (DLT) occurs move to the next level of 2 x 300 mg ITRA which will be considered the MTD.

or

e) Three patients will receive the initial dose of 2 x 200mg ITRA if one DTL occurs the cohort will expanded to six patients. If no further DTL occurs in the additional patients the dose will be expanded to 2 x 200mg ITRA which will be considered the MTD. If one or more DTL occurs the MTD is reached.

or

f) Three patients will receive the initial dose of 2 x 200mg ITRA if two or more dose-limiting toxicity occurs the MTD is reached.

Third cohort – 2 x 300 mg ITRA

a) **Three patients** will receive the dose of 2 x 300 mg ITRA only if no DLT occurred in patients who received 2 x 200 mg

or

b) Three patients will receive the dose of 2 x 300 mg ITRA if only one DLT occurs in a cohort of six patients

4.4 Dose Limiting Toxicity

Non-Haematological DLT deemed by the local investigator and/or Sponsor to be related to treatment will be defined as the following:

- Any treatment-related Grade 4 non-haematologic (non-laboratory) AE
- Any treatment-related Grade 3 non-haematologic clinical (non-laboratory) AE (except fatigue) lasting >3 days despite optimal medical intervention
- Grade ≥3 non-haematologic laboratory abnormality if:
    - Medical intervention is necessary to treat the patient, or
    - The AE led to the patient being hospitalised, or
    - The AE persists for ≥ 7 days.

Any adverse event (deemed by the local investigator and/or Sponsor to be not-related to treatment) that leads to 7 or more dose omissions during the first 28 days from dose administration

If patients experience a DLT with an onset date during the first 12 days ITRA administration should be permanently discontinued. DLTs are an adverse events of special interest (AESI) and must be reported on the SAE-Sheet **within 24 hours of becoming aware of the event**.

IMP Logistics und Accountability / *IMP Logistik und Verantwortung*

4.5.1 Delivery, storage, allocation and destruction / *Belieferung, Lagerung, Zuweisung und Vernichtung*

The entire process regarding the IMP is carried out between the responsible project manager and monitor of the KKS Magdeburg (KKS), the central pharmacy of the University Hospital A.ö.R. Magdeburg and the
4.5 principal investigator at the trial site.

The IMP is stored during the CT at room temperature (max. 25°C) at the trial site in a lockable cabinet.

The study nurse documents the room temperature once a week in a temperature log.

Unused IMP is returned to the pharmacy by the monitor and destroyed in accordance with the pharmacy´s internal guidelines. The destruction protocol is stored in the Trial Master File (TMF).

4.5.2 Drug Accountability

The monitor will check the drug accountability records in the PZ to ensure the correct allocation of the study medication and compliance as described in the trial specific monitoring plan.

Treatment Compliance / *Behandlungscompliance*

4.6 The participants receive a counted amount of IMP in the original blister pack to take home and take it independently. To obtain study-relevant data, patients should take:

First cohort - 2 x 100 mg ITRA – at least 80 tablets ITRA (planned 94 tablets)
Second cohort – 2 x 200 mg ITRA – at least 160 tablets ITRA (planned 188 tablets)
Third cohort - 2 x 300 mg ITRA – at least 240 tablets ITRA (planned 282 tablets)

The patients have to return the empty and/or remaining blister packs at the end of the treatment.

An additional medication plan will be provided to the participants to the taking of the IMP.

5

5.1 Aims of the clinical trial / *Ziele der klinischen Prüfung*

Primary aim / *Primäres Ziel*

5.2 To determine the maximum tolerated dose (MTD) of ITRA given concurrently with RT and TMZ.

Secondary aims / *Sekundäre Ziele*

- To determine the safety profile of ITRA given concurrently with RT+TMZ as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version
5.3 5.0
- To determine the effect of ITRA given concurrently with RT+TMZ on overall survival (OS)
- To assess the tolerability of treatment regimen
- To evaluate patient reported health related quality of life outcomes

Endpoints / *Endpunkte*

5.3.1 Primary Endpoint /*Primärer Endpunkt*

To determine the maximum tolerated dose (MTD) of ITRA given concurrently with RT+TMZ .

5.3.2 Secondary endpoints / *Sekundäre Endpunkte*

- Safety and tolerability of ITRA given concurrently with RT+TMZ
- Overall survival (OS)
- Progression-free survival (PFS)
- Best Overall Objective Response Rate
- Use od Corticosteroids
- Treatment compliance
- Health-related Quality of life (HRQoL - EORTC Quality of Life Questionnaire (QLQ)-C30 and Brain Cancer Module (BN20))

Description of the clinical trial / *Beschreibung der klinischen Prüfung*

6 Design of the trial / *Studiendesign*

6.1

The planned CT is a non-commercial investigator-initiated, monocentric, prospective, CT according to ICH E8 (R1) (IIT) of phase I.

Treatment design / *Behandlungsdesign*

6.2

6.2.1 RT with concomitant TMZ – standard of care / *RT mit begleitender TMZ – Standardtherapie*

RT treatment must begin > 2 weeks and ≤ 4 weeks after surgery.

RT will be given daily five days per week (Monday through Friday) over a period of six weeks at a dose of 2 Gy per fraction for a total dose of 60 Gy. Volumetric Intensity Modulated Arc Therapy (VMAT) will be delivered with linear accelerators with nominal energy of 6 megavoltages (MV) or more.

Postoperative MRI imaging will be fused with planning CT to define a gross tumor volume (GTV). Contrast-enhanced T1 as well as T2 (in case of secondary GBM) will be used. Treatment verification and documentation will be carried out weekly with cone-beam CT.

Surgical cavity and T1 enhancing lesion will be fused and expanded 1.5 cm and adapted according to anatomical borders and organs at risk (OARs) to define the clinical target volume (CTV). In case of secondary GBM, non-enhancing T2 component will be expanded 1 cm to create a CTV. Planning target volume (PTV) will be created by 0.4 cm expansion of CTV. OAR will include the lenses of both eyes, both optic nerves, the optic chiasm, and the brainstem and dose constraints to these OAR will be:

Dose constraints

Optic Chiasma and Nerves D_{max}	< 54 Gy
Retina D_{max}	< 45 Gy
Brainstem D_{max}	< 54 Gy
Cochlea D_{mean}	< 50 Gy
Pituitary Gland D_{max}	< 50 Gy
Lens D_{max}	< 10 Gy
Lacrimal gland D_{max}	< 40 Gy
Hippocampus	< 9 Gy (if reasonably achievable)

TMZ treatment will commence from first day of treatment with RT and will be administered continuously (including weekends) until the last day of RT at a daily oral dose of 75 mg/m^2 for a maximum of 42 days. The TMZ dose will be calculated using actual body surface area (BSA Patients should start ITRA therapy 5 days before the start of scheduled RT + TMZ. TMZ should be taken in the morning on the empty stomach.

6.2.2 ITRA during concomitant RT + TMZ / *ITRA während gleichzeitiger RT + TMZ*

Treatment with ITRA should start 5 days before RT+TMZ treatment. ITRA should be taken daily (including weekends) 2-3 hours before planned radiotherapy together with TMZ until the last day (including) of radiotherapy. Morning dose of ITRA should be taken immediately after a full meal. In patients with reduced gastric acidity, such as patients taking H2-receptor antagonists or proton pump inhibitors (PPI) or subjects with achlorhydria caused by other diseases, ITRA will be administered under fasted conditions with a an acidic beverage (such as a non-diet cola) after pretreatment with a H2-receptor antagonist. Evening dose of ITRA should be taken immediately after a full meal in subjects without reduced gastric acidity otherwise ITRA should be taken under fasted conditions with an acidic beverage (such as a non-diet cola) after pretreatment with a proton pump inhibitors. During weekends without RT (Saturday and Sunday), TMZ and ITRA will be taken as described previously.

6.3 Treatment delay and interruption / *Verschiebung und Unterbrechung der Behandlung*

Treatment will be interrupted or discontinued for adverse events, as described below. Any dose reduction or modification for TMZ and ITRA will not be allowed. If RT is interrupted for ANY reason for > 1 week, the patient will be excluded from this study. If treatment with TMZ or ITRA is interrupted for ANY reason for > 1 week, the patient will be excluded from this study.

6.3.1 TMZ during concomitant RT / *TMZ während gleichzeitiger RT*

About delay or discontinuation of TMZ treatment will be decided weekly based on the hematologic and non-hematologic adverse events (AEs), described in the Temodal European Public Assessment Report – Product information. If the administration of TMZ must be interrupted for any reason related to treatment with this drug, the RT and ITRA administration should continue normally. Missed doses of TMZ will not be made up at the end of RT. In case of TMZ treatment interruption lasted > 1 week, patient will not be treated according to this protocol and she/he will be allocated to standard treatment.

6.3.2 ITRA during concomitant RT + TMZ / *ITRA während gleichzeitiger RT + TMZ*

Based on adverse events, the same criteria for delay or interruption of the treatment with ITRA will be used as described for treatment with TMZ.

Additionally, treatment with ITRA will be delayed/continued or interrupted in case of the appearance of adverse events related to this drug such grade 3 or 4 hypokalaemia or hypertension.

If the administration of ITRA must be interrupted for any reason related to the treatment with this drug, the RT and TMZ administration should continue normally.

Missed doses of ITRA will not be made up at the end of RT.
In case of ITRA treatment interruption lasted > 1 week, patient will not be treated according to this protocol and she/he will be allocated to standard treatment.

6.3.3 RT delay / *RT Verschiebung*

In case of the temporarily interruption of radiotherapy (≤ 1 week) due to medical or technical reasons unrelated to the treatment with temozolomide and ITRA, daily administration of both drugs will continue.

6.4 Treatment of symptoms of increased intracranial pressure / *Behandlung der Symptome eines erhöhten Hirndrucks*

In GBM patients, dexametasone is standardly used for symptomatic treatment of increased intracranial pressure. ITRA is an inhibitor of cytochrome P450 3A4. It has been reported that ITRA markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect **[39]**. Based on this fact, in this trial treatment with dexamethasone will not be allowed. Subjects requiring steroid medication to treat symptoms of increased intracranial pressure will be treated with prednisolone due to fact that ITRA has no effect on prednisolone pharmacokinetics **[40]**. Dose of prednisolone will be calculated using online Corticosteroid Conversion Calculator http://clincalc.com/corticosteroids/Data on medication with corticosteroids, antiepileptics and analgesics will be recorded in the Case Report Form until the last Follow up visit.

6.5 Course of trial / *Studienablauf*

Planned Start: Q4/2024 - Real date of Initiation Visit must be reported in CTIS
Planned FPFV: Q4/2024 - Real date must be reported in detail in CTIS
LPLV: Q4/2025
End of CT: Close-out-Visit (COV), after final data collection/documentation in the CRF according to LPLV and final follow-up of open points

After a neurosurgical operation or biopsy, the neurosurgeon will inform the potential participants about this study. He will give them the patient information about this CT. If they decide to participate, they will sign a consent form during Visit 1 at the trial site.

Visit 1:

- Patient information and Informed Consent
- Inclusion and Exclusion Criteria
- Specific medical history including current medication
- Physical examination
- Performing an ECG (part of clinical routine)
- Blood sampling for general health assessment:
  - AST, ALT, bilirubin, sodium, potassium, hemoglobin, complete blood count including leukocytes, neutrophils, lymphocytes, thrombocytes and erythrocytes and

- ACTH, *but only* if the participants has to take prednisolone from the start of the CT
- BMI
- HRQoL- EORTC Quality of Life Questionnaire (QLQ)-C30 and Brain Cancer Module (BN20)

Visit 2 (within 7 days after V1):

- Planning Standard Treatment (RT + TMZ)
- Providing and start taking ITRA and filling the medication plan
- Inquiry AE and SAE

Visit 3 (within 5 days after V2):

- Starting Standard Treatment
- Inquiry AE and SAE

Visit 4 (7 days +/- 1 day after V3):

- Blood sampling for general health assessment see visit 1
- Inquiry AE and SAE

Visits 5 – 7 weekly (+/- 1 day):

- Blood sampling for general health assessment see visit 1
- Inquiry AE and SAE

Visit 8 (7 days +/- 1 day after V7):

- Physical examination
- Blood sampling for general health assessment see visit 1
- BMI
- Inquiry AE and SAE

Visit 9 (7 days +/- 1 day after V8):

- End of completed standard treatment + ITRA
- Return of the empty and/or remaining blister packs
- Blood sampling for general health assessment see visit 1
- Performing an ECG (part of clinical routine)
- HRQoL - EORTC Quality of Life Questionnaire (QLQ)-C30 and Brain Cancer Module (BN20)
- Inquiry AE and SAE

In General:

ACTH determination independent of the visit only if the participants develop symptoms of increased intracranial pressure during treatment and treatment with prednisolone is required, then at the following visit

Tabular overview of all examinations carried out on the patients during the CT.

	Visit 1	**Visit 2** (within 7 days after V1)	**Visit 3** (within 5 days after V2)	**Visit 4** 7 days (±1 day) after V3	**Visit 5** 7 days (±1 day) after V4	**Visit 6** 7 days (±1 day) after V5	**Visit 7** 7 days (±1 day) after V6	**Visit 8** 7 days (±1 day) after V7	**Visit 9** 7 days (±1 day) after V8
Patient information and Informed Consent	√								
Inclusion and Exclusion Criteria	√								
Demographic Data	√							√	
Medical History/ Comorbidities	√								
Comedications	√								
ECG	√								√
Blood sampling	√			√	√	√	√	√	√
Vital signs/BMI	√								√
Start IMP (ITRA), ongoing until V9		√							
AEs and SAEs		√	√	√	√	√	√	√	√
HRQoL	√								√

6.5 Early termination of the clinical trial / *Frühzeitiger Abbruch der klinischen Prüfung*

Everyone involved is aware that the safety of the participants is the top priority when conducting CT. The auditors will therefore report any identifiable risks to the affected persons to the sponsor at any time within 48 hours of becoming aware of them.

If an auditor has general ethical concerns about the continuation of the CT, this must be reported to the main auditor immediately.

Taking the approved investigational drug does not suggest any serious unexpected side effects and discontinuation of the entire CT is considered unlikely. Possible side effects/adverse events are systematically recorded.

The principal investigator and/or the sponsor are entitled to terminate the CT early due to relevant medical but also regulatory reasons. The reasons for the termination of the CT are documented in detail.

Reasons for an examiner to cancel the CT for the examination participants can be:

- continued participation in the CT is no longer medically justifiable,
- the entire CT is canceled,
- occurring side effects or contraindications,

The sponsor is still entitled to terminate the CT early for the following reasons:

- the sponsor-investigator agreement is not adhered to,
- participant recruitment is inadequate,
- Non-compliance of the trial site,
- serious problems with the quality of the collected data that cannot be clarified arise,
- unforeseeable circumstances arise in the trial site that do not allow the CT to continue,

- unacceptable risks and toxicities occur (decision after a new benefit-risk assessment),
- new scientific findings during the term of the CT do not allow its continuation,
- further financing of the CT is not guaranteed.

Requirements on PZ and Investigators / *Anforderungen an Prüfzentren und Prüferinnen/Prüfer*

6.6 The members of the trial team are selected by the principal investigator. The respective functions/responsibilities are defined in the delegation log. He appoints a representative who should be just as qualified as himself. Recruitment and execution takes place in the radiation clinic of the University Hospital Magdeburg A.ö.R.

Safety-Management / *Erfassung der Sicherheit*

7 The process and coordination of reporting and deadlines between the sponsor and the trial site is described in detail here.

Definitionen

7.1

AE **CTR Article 2 (32)**	**'Adverse event'** means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment;
ADR **ICH E6 (R2) (1.1)**	In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function
SAE **CTR Article 2 (33)**	**'Serious adverse event'** means any untoward medical occurrence that requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death
(S)ADR **ICH E6 (R2) 1.50**	**Serious Adverse Drug Reaction (Serious ADR)** Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity,

	or is a congenital anomaly/birth defect.
SUSAR **CTR Article 2 (34)**	Suspected `Unexpected Serious Adverse Reaction' means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information;
UADR **ICH E6 (R2) 1.60**	An AR, the nature or severity of which is not consistent with the applicable product information (SmPC)

7.2 Expected drug reactions of Itraconazole / *Erwartete Nebenwirkungen von Itraconazole*

The most common drug reactions of ITRA are gastrointestinal disturbances, such as nausea, mild diarrhea, vomiting, and abdominal pain. Other reported side effects which can be related to treatment with ITRA are generalised edema, hypertension, headache, abnormal hepatic function, hypokalemia fatigue, fever, malaise, rash, pruritus, impotence, somnolence, albuminuria, erectile dysfunction.

Drug reactions related to treatment with ITRA will be treated as per standard institutional policy.

7.3 Contraindicated drugs for co-administration with ITRA / *Kontraindizierte Arzneimittel zur gleichzeitigen Anwendung mit ITRA*

Contraindicated drugs for co-administration with ITRA are:

ergot alkaloids, irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ranolazine, eplerenone, cisapride, lovastatin, simvastatin.

7.4 Not recommended drugs for co-administration with ITRA / *Nicht empfohlene Arzneimittel zur gleichzeitigen Anwendung mit ITRA*

Not recommended drugs for co-administration with ITRA are:

dasatinib, nilotinib, aliskiren, everolimus, temsirolimus, salmeterol, vardenafil, colchicine.

7.5 Drugs which should be co-administered with ITRA with caution / *Arzneimittel, die zusammen mit ITRA mit Vorsicht verabreicht werden sollten*

Drugs which should be co-administered with ITRA with caution are:

coumarins, cilostazol, dabigatran, repaglinide, saxagliptin, praziquantel eletriptan bortezomib,busulphan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids, alprazolam, aripiprazole, buspirone, diazepam, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone, maraviroc, indinavir, ritonavir, saquinavir, nadolol, other dihydropyridines, verapamil, aprepitant, budesonide, ciclesonide, cyclosporine, dexamethasone, fluticasone, methylprednisolone, rapamycin, tacrolimus, atorvastatin, fesoterodine, sildenafil, solifenacin, tadalafil, tolterodine, cinacalcet, tolvaptan

If patients of this CT are treated with any of the contraindicated drugs before entering the trial, during this CT they will be treated with alternative drugs used for the same indication.

7.6 Reporting and obligations/*Meldungskaskade und –verpflichtungen*

These are carried out in accordance with the provisions of the CTR in Articles 40 to 43.

7.6.1 Reporting of adverse events and serious adverse events by the investigator to the sponsor / *Mitteilungspflichten der Prüfer*

7.6 1. The investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.

2. The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently. The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

3. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

4. If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

The investigators must inform the KKS SAE Manager immediately (without undue delay, i.e. within 24 hours for the sponsor) about the occurrence of a SAE (initial report) after the awareness at the site. The report is made by the investigator responsible in the Delegation Log authorized by the PI by Email with scan using the SAE reporting form provided by the sponsor. The investigator must then submit a detailed FU report on the reported SAE to the KKS MD until the SAE is completed.

SAEs will be followed up for one week after the LPLV (V9) for each patient.

7.6.2 Second Assessment / *Zweitbewertung*

The assessment of a possible causal relationship to the test medication and the assessment of whether this is expected or unexpected according to the reference document, in this case the current product information (SmPC), is first carried out by an investigator. An additional second assessment by the sponsor is carried out by two qualified independent physicians of the clinic. Both take note of all relevant study documents that are necessary for the assessment as well as the requirements for reporting and deadlines and documentation. The reporting deadline of 48 hours must be observed so that the sponsor can meet its SUSAR reporting obligation to the relevant institutions. The SAEs are sent to the second assessors by email for assessment. The original assessments are filed by the second assessors in a

separate folder. They are collected by the monitor for filing in the TMF at the end of the CT at the latest during the close-out visit. Copies are available in the TMF during the CT.

7.6.3 Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency / *Mitteilungspflichten des Sponsors*

The sponsor of a clinical trial performed in the Member State shall report electronically and without delay to the database referred to in CTR Article 40(1) all relevant information about the following suspected unexpected serious adverse reactions:

(a) all SUSARs to the IMP occurring in that CT

(b) all SUSARs to the IMP occurring in any of the subjects of the CT, which are identified by or come to the attention of the sponsor after the end of the CT.

2. The period for the reporting of SUSARs by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:

(a) in the **case of fatal or life-threatening** SUSARs, as soon as possible and in any event **not later than seven days after the sponsor became aware** of the reaction;

(b) in the **case of non-fatal or non-life-threatening** SUSARs, **not later than 15 days after the sponsor became aware** of the reaction;

(c) in the case of a SUSAR which was initially considered to be non-fatal or non- life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening. Where necessary to ensure timely reporting, the sponsor may submit an initial incomplete report followed up by a complete report.

7.6.4 Re-examination of the benefit-risk assessment / *Erneute Überprüfung der Nutzen-Risiko-Bewertung*

A re-examination of the CT with regard to the benefit-risk assessment of the IMP/CT is necessary if:

- individual case reports of suspected expected serious adverse reactions (SESARs) with an unexpected outcome,
- an increase in the frequency of SESARs that are assessed as clinically relevant,
- SUSARs that arose after the participant had already completed the CT,
- events related to the conduct of the CT that could potentially affect the safety of the participants.

7.6.5 Annual Safety Report (ASR) / *Jährlicher Sicherheitsbericht*

The sponsor shall submit annually through the database referred to in Article 40(1) to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.

The ASR shall only contain aggregate and anonymised data.

The obligation starts with the first authorisation of the CT in accordance with the CTR. It ends with the end of the CT.

The ASR is prepared in collaboration with the investigator in accordance with the requirements of the “ICH guidline E2F on development safety update report”.

7.6.6 Measures to protect against immediate danger / *Maßnahmen zum Schutz vor unmittelbarer Gefahr*

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

7.7 Documentation / *Dokumentation*

7.7.1 Documentation of AEs / *Dokumentation von AEs*

All AEs, including acute illnesses that occur during the treatment of another illness during an inpatient stay but are not caused by the underlying illness are documented. These must be documented in the original subject file and then in the paper CRF on the page provided for this purpose by the study nurse/investigator.

If an AE occurs, the affected person must be observed until the symptoms have subsided or pathological laboratory values have returned to baseline values, or until the investigator believes that no further findings are to be expected. If the adverse event results in a persistent secondary illness, this is to be classified as an SAE and documented accordingly at the end of the CT. All findings and results must be documented in both the subject file and the paper CRF. The AEs are continuously documented in an AE line listing at the trial site and made available to the sponsor at the end of the CT or upon request for filing in the TMF. Cases of overdose, abuse, application errors, etc. should be documented, even if an AE does not occur.

The following information is necessary:

- Type of AE (sign, symptom or disease, if possible diagnoses),
- Assessment of (worsening of existing) concomitant diseases as AE,
- Differentiation (serious/not serious),
- Start, knowledge by the investigator and end of the AE (outcome),
- Degree of severity (mild, moderate, severe),
- Causality to the test product possible? Measures regarding the test product or actions to restore or improve the well-being of the affected person,
- SAE yes or no.

7.7.2 Documentation of SAEs / *Dokumentation von SAEs*

All SAEs must be documented for the study participant from the time the informed consent is signed until the end of the CT.

The responsible clinical monitor must check the data at the trial site for completeness and ensure that the information in the SAE report matches other data sources and has been reported to the sponsor on time.

The sponsor maintains a SAE line listing.

Emergency Contact / *Notfallkontakt*

In medical emergencies, study participants should contact the Department of Radiation Oncology at Magdeburg University Hospital directly during regular working hours (08:00 - 16:30): 0391 67 15 788

7.8 In medical emergencies outside these working hours, participants of this clinical trial should present themselves at our emergency department: Leipziger Straße 44, 39120 Magdeburg.

Documentation of the data / *Dokumentation der Daten*

8 It is the responsibility of the principal investigator to ensure that the CT is carried out in accordance with the GCP guideline, the CTR, the AMG and the trial protocol, and that the data is correctly entered into the paper CRF. All data collected in this CT must be entered into the CRF by personnel appropriately authorized in the delegation log. This also applies to data from people who have been excluded from the CT.

The investigators note the participation on a special identification list. It serves to enable the participants to be identified later and contains a participant ID, full name, date of birth and the date of inclusion in the CT. The identification list remains in the Investigator Site File (ISF) after the CT has been completed. In addition, the inclusion of the participants must be noted in the original subject file (source data) (date/time of inclusion including information/consent, patient ID, end of CT).

8.1 An enrollment log is also kept at the trial site, where only the patient ID, as well as the date of consent, the version of the patient information/declaration of consent, and the exclusion/end (early/regular) are documented. A copy of this list will be filed with the sponsor at the end of the KC in the TMF.

Case Report Form (CRF) / *Erhebungsbogen*

As part of this CT we work with a paper CRF. The CRFs may only be filled out with a ballpoint pen, preferably blue. Corrections must be made in such a way that the old entry remains legible (the use of correction materials is not permitted). Corrections must be hand-signed and dated by the authorized person making them. If it is not clear why the change was made, a brief explanation must be noted. Data that is not available or has not been collected must be clearly identified. The reasons for this must be documented. The investigator ensures that all data are entered into the CRFs promptly, legibly, completely, correctly and in accordance with the original subject files. After a final check for plausibility and completeness by the monitor and approval by the principal investigator, the final completed original pages are collected for evaluation by the statistician and finally for filing in the TMF. A copy remains at the trial site and is kept there for 25 years.

Investigator Site File (ISF) / *Prüfarztordner*

The trial-specific ISF will be made available to the trial site by the sponsor at the latest for initiation and will be discussed there with everyone involved. The documents required for the CT are stored here (according to ICH Guideline E6 (R2) – Essential Documents, Appendix 8). As part of the monitoring, the ISF is checked for timeliness and completeness in accordance with the regulations.

8.2

8.2.1 Retention obligations of the principal investigator / *Aufbewahrungspflichten des Hauptprüfers*

After completing or discontinuing the CT, the ISF must be kept for at least 25 years. The originally signed consent forms are stored in the ISF at the trial site for the legally required retention period (25 years). The source data are stored for 25 years.

8.2.2 Retention obligations of the sponsor / *Aufbewahrungspflichten des Sponsors*

After completion of the CT, the TMF will be archived by the sponsor for 30 years.

9 Statistics / *Statistik*

The statistical analysis is carried out by a statistican of the IBMI. Together with the PI and PM the statistical results report for the final study report, which is submitted by the sponsor via the CTIS, will be prepared.

9.1 Statistical analysis / *Statistische Analyse*

Primarily, the maximum tolerated dose (MTD) should be determined together with information about all side effects (drug reactions) and toxicities. The effect on the tumor (response), tolerability and quality of life are considered secondary. All relevant analyses are primarily descriptive.

9.2

9.3 Sample Size Planning / *Fallzahlplanung*

We plan to apply the classical 3+3 design in order to determine the MTD of ITRA (see Chapter 3.3; 4.3).

Endpoints / *Zielgrößen*

The occurrence of dose-limiting toxicities (DLT) (see Chapter 4.6), defined as the primary endpoint, is documented in connection with the dose given. Results of the blood tests for the individual visits provide additional information about safety, tolerability and response. In addition, parameters for health-related quality of life (HRQoL) are collected at the beginning and end.

9.4

Datenanalyse

The analysis begins with the descriptive description of the demographic and anamnestic data, the examination data (the clinical neurological, physical and blood tests) before the start of treatment and the quality of life parameters at that time. Frequencies are calculated for qualitative characteristics and

presented as absolute numbers and percentages. Position and dispersion parameters are determined for quantitative characteristics. The results of the corresponding study variables over time or at the end of the treatment are also recorded descriptively.

The primary endpoint - the occurrence of dose-limiting toxicities - is listed in detail in a table with reference to the respective dose given. All other side effects are also documented in detail.

Regarding the secondary parameters, any differences in values between the start and end of treatment can be examined using paired sample tests. In addition, variance analysis methods can be used to display the results of blood tests over time.

Datenbankschluss / Data Base Log

The final data capture in the CRF is completed with LPLV.

9.5 After a final check for plausibility and completeness by the monitor and final approval by the principal investigator, the final completed original pages are collected for evaluation by the statistician and finally for filing in the TMF.

The PZ retains copies of the final CRFs for overall evaluation.

Ethical, legal and administrative aspects / *Ethische, rechtliche und administrative Aspekte*

10

This CT is carried out in accordance with the Declaration of Helsinki (2013), the currently European EU regulation/CTR, ICH-E6 (R2) GCP, and the current German AMG.

10.1 Sponsor and Principal Investigator Responsibilities / *Verantwortlichkeiten von Sponsor und Hauptprüfer*

In accordance with CTR Art. 2, No. 14; Art. 71 and AMG § 4 (24), the sponsor of this CT assumes responsibility for initiating, organizing and financing the CT to be carried out. The sponsor and principal investigator ensure that the CT is carried out in accordance with existing laws and regulations, in accordance with ICH-E6 (R2) and the Declaration of Helsinki (2013). All investigators accept the requirements and sign this protocol. Responsibilities are defined in a trial-specific sponsor-investigator agreement and are partially delegated to the principal investigator.

10.2 In accordance with CTR Art. 2, No. 16; Art. 73 and AMG § 4 (25), the principal investigator assumes responsibility for carrying out the CT at the trial site.

Submission in CTIS / *Einreichung im CTIS*

The modalities of the initial submission are prescribed in the CTR and exclusively in the CTIS in the sponsor workspace. The CT admin enters the relevant information and documents. When printed, the document is not subject to the update service

A distinction is made between submissions in Part I and Part II.

All relevant documents and their contents are listed in Appendix I of the CTR.

The sponsor informs about the start of the CT via the CTIS. This notification is made within 15 days of the start of the CT. Furthermore, the inclusion of the first patient must be reported (First Patient First Visit/FPFV).

Patient Information and Informed Consent / *Patienteninformation und Einwilligungserklärung*

The information and consent process corresponds to the informations submitted in the *Recruitment and Informed consent template* (EudraLex Vol 10.)

10.3 Before the start of the CT, each patient must give written consent to an investigator authorized in the delegation log, after they have previously been given oral and/or written information about the nature, meaning and scope of the CT in a way that they can understand. Potential participants (or their legal representatives) will have between 5 and 7 days to decide whether to participate in this study. The declaration of consent to participate in the CT is handwritten with the date and signature of the patient and the investigator. A copy of the signed patient information/consent form will be given to the participating patient, and the original will be stored in the ISF. It is expressly pointed out that no examinations in connection with the CT may be carried out until a legally valid declaration of consent has been given. If the content of the patient information changes during the CT due to necessary amendments, it must be checked which patients then have to read the new version again and give their consent to the changed circumstances again.

10.4 Insurance / *Patientenversicherung*

On behalf of the sponsor, the mandatory insurance in accordance with § 40a, Nr.3 AMG was taken out for all participants with the following insurance:

Name and Adress of the Ensurance:

Telefon:
Fax:

Versicherungsscheinnummer:

This means that trial-related damage to health is insured with a maximum coverage of 500,000 euros per participant. This insurance covers all possible damage that the participant suffers directly or indirectly as a result of the investigational drug or interventions in connection with the CT. Only material damage will be compensated. In order not to jeopardize insurance coverage, patients participating in the CT must strictly follow the trial protocol. Furthermore, they are not allowed to undergo any other medical treatment during the CT without the consent of the investigators (except in emergencies). You must inform the examiners immediately about any emergency treatment. Participating patients must immediately report any damage to their health that could have occurred as a result of the CT to the investigators and the insurance company. In addition, the participating patients must take all appropriate measures to clarify the cause and extent of the damage that has occurred. In a personal conversation, the patient is explained in detail and understandably by an investigator about the process as well as the meaning, risks and scope

of the CT. The participating patient receives the insurance conditions together with the patient information and a copy of the signed consent form.

Data protection and confidentiality / *Datenschutz und Schweigepflicht*

The collection, transfer, storage and evaluation of personal data within this CT is carried out in accordance with the current legal regulations (General Data Protection Regulation/GDPR and State Data Protection Act of Saxony-Anhalt). The prerequisite for this is the voluntary consent of the participants as part of the
10.5 declaration of consent before taking part in the CT. They will be informed of the following within the information/consent about this CT:

1. that as part of this trial, personal data, in particular information about his health and ethnic origin, will be collected and recorded in paper form and on electronic data carriers in the radiotherapy clinic.

2. that the data collected from you will be passed on in pseudonymized form, if necessary, to:

1) the sponsor Otto-von Guericke University Magdeburg, Medical Faculty, Leipziger Str. 44, 39120 Magdeburg

2) and by this to commissioned bodies for the purpose of implementation and scientific evaluation,

3) in the event of adverse events: - to the sponsor, - and by this, if necessary, to the competent authorities of the member states of the European Union or the Agreement on the European Economic Area in whose territory the above-mentioned clinical trial is being carried out - or to the European database set up for monitoring drug safety (EudraVigilance), to which the competent supervisory authorities throughout the European Union and the European Economic Area have access.

The data collected and stored by you as part of the above-mentioned clinical trial (including the original clear data) can, if necessary and legally permitted, be viewed by the responsible competent supervisory authority as part of inspections or by representatives of the sponsor (so-called auditors or monitors) to check that the clinical trial is being carried out properly in the trial center. They are obliged to maintain confidentiality and the data collected will not be passed on in this context. As part of this clinical trial, your pseudonymized data will only be passed on within the European Union and the European Economic Area for the purposes of data evaluation, approval and monitoring.

4. that participation in the CT can be stopped at any time. However, consent to the collection and processing of personal data, in particular health information, is irrevocable. It is known that in the event of a withdrawal from participation in the CT, the data stored up to this point may continue to be used to the extent necessary

a) determine the effects of the medication to be tested,

b) to ensure that my legitimate interests are not impaired,

5. that the data will be retained for at least 30 years after the CT has been completed or discontinued, as determined by the regulations governing drug trials. The personal data will then be deleted unless statutory, statutory or contractual retention periods conflict with this.

6. that if the consent to participate in the study is revoked, all bodies that have stored the personal data, in particular health data, must immediately check to what extent the stored data is relevant to the purposes mentioned in No. 4 a) to b). Purposes are still necessary.

Data that is no longer required must be deleted immediately.

Modifications and deviations of the protocol / *Änderungen und Abweichungen des Prüfplans*

Modifications of the protocol / *Änderungen am klinischen Prüfplan*

11 If modifications are made to the protocol, it will be checked whether the modification is a substantial modification or not. If the modification is substantial, the protocol will be submitted again to CTIS for approval for a new decision.

11.1

11.1.1 Substantial Modifications / *Wesentliche Änderungen*

Any change to any aspect of the CT, after notification of one referred to in CTR Articles 8, 14, 15, 19, 20 or 23 decision is made and is likely to have a significant impact on the safety or rights of participants or reliability and reliability of the data obtained as part of the CT.

Examples:

- General decision on the conduct of the CT,
- Adding a trial site or changing the PI on the trial site.

11.1.2 Non-Substantial Modification / *Unwesentliche Änderungen*

The Sponsor will continually update the EU database with any changes to the CT, which are not substantial modifications, but are relevant for the monitoring of the CT.

Examples:

- Change in the number of participants,
- Change of persons/entries and contact details to those delegated by the sponsor tasks,

11.2

- Extension of validity of insurance documents

Deviations of the protocol / *Abweichungen vom Prüfplan*

A deviation represents the difference from the regulatory reference and extends to structural, organizational, trial-independent and trial-specific deviations or errors and erroneous behavior. It is always a deviation as soon as action tracking is required. Deviations that occur during the conduct of the CT at the trial site must be documented by the site and reported to the sponsor using a trial site deviation form. The monitor checks these during the monitoring visits. The deviations must be filed in the TMF and ISF. The resulting measures will be communicated with the trial team. This also applies to a deviation from a process prescribed by a SOP (e.g. Site-SOP) or guides.

Serious Breaches / *Schwerwiegende Verstöße*

A “serious breach” according to Article 52 CTR

is a breach of security and safety rights of a participant or the reliability and resilience of the data obtained from the CT is likely to be significantly compromised.

A potential serious breach can be reported by any member of the trial site or the KKS. These findings can
11.3 be through meetings, notices, complaints, central or site-based monitoring, audits or routine review of general compliance with regulations.

The 7-day period begins with the acknowledgment at the Sponsor-QM. To ensure that all necessary information is included in the CTIS, the KKS Form Serious Breach Notification is used.

It will then be decided together with everyone involved whether it is really one Serious Breach is involved. Information about possible serious breaches will be kept confidential treated.

For further information also will be used the “Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol” including examples for serious breaches.

Qualityassurance / *Qualitätssicherung*

12 Monitoring and audits are carried out as part of quality control and assurance of the Sponsor/KKS to ensure that the CT is carried out in a GCP-compliant manner.

12.1 Monitoring

The monitoring is carried out by the KKS. It is carried out risk-based according to a trial-specific monitoring plan and includes the monitoring of the progress of the CT and ensuring that it is carried out, documented and reported in accordance with the protocol, SOPs and applicable legal regulations.

12.2

Audit

In order to ensure the conduct of the CT in accordance with GCP guidelines, audits are carried out by the sponsor QM at least once a year. The sponsor can also commission external authorized institutions to carry out audits. The auditor is independent of the people involved in the CT, but is not an authority.

After each audit, the principal investigator receives an audit report on which to comment and, if necessary, an action plan that must be processed. After the deficiencies have been corrected, the trial site receives an audit certification. The audit report will be made known to the sponsor of the CT. Audit certificate must
12.3 be stored in the ISF and TMF and be available in the event of an inspection by the responsible authority. The audit report must be kept independently of ISF and TMF.

Inspection / *Inspektion*

Inspections at the sponsor for a specific CT and/or a participating trial site in this CT can be carried out by responsible authority in accordance with the German AMG. This can be routine, but it can also take place on an occasion-related basis.

Publication policy / *Veröffentlichungspolitik*

Before recruitment begins, the CT is registered in the German Register of Clinical Studies (DRKS) as the WHO's German primary registry by the KKS-PM.

The sponsor shall notify of the start of a CT through CTIS. That notification shall be made within 15 days.
13

The sponsor shall notify of the first visit of the first subject through CTIS. That notification shall be made within 15 days from the first visit of the first subject.

End of Trial / *Beendigung der KP* and / *und* Summary of the CT */Abschlussbericht der KP*

13.1 The end of the CT is defined with the COV by the monitor.

The sponsor shall notify of the end of the CT through the CTIS. That notification shall be made within 15 days from the end of the CT.
Irrespective of the outcome of the CT, within one year from the end of the CT the sponsor shall submit to the EU database a summary of the results of the CT. The content of that summary is set out in Annex IV of the CTR.
It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V of the CTR.

13.2

Publications / *Publikationen*

The data are the property of the sponsor. He undertakes not to use the data commercially and not to allow third parties to use this data commercially.
The sponsor has unrestricted publication rights to the data.
The sponsor/principal investigator is permitted to publish the scientific results obtained after the
14 completion of the CT, even if the investigational product shows an unexpected effect.

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Attachement 1

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Ziemlich**	**Sehr**
31. Fühlten Sie sich unsicher in Bezug auf die Zukunft?	1	2	3	4
32. Hatten Sie das Gefühl, gesundheitliche Rückschläge erlitten zu haben?	1	2	3	4
33. Waren Sie besorgt, dass Ihr Familienleben gestört werden könnte?	1	2	3	4
34. Hatten Sie Kopfschmerzen?	1	2	3	4
35. Hat sich Ihre Einstellung zur Zukunft verschlechtert?	1	2	3	4
36. Haben Sie doppelt gesehen?	1	2	3	4
37. Haben Sie verschwommen gesehen?	1	2	3	4
38. Hatten Sie Schwierigkeiten beim Lesen?	1	2	3	4
39. Hatten Sie Anfälle?	1	2	3	4
40. Hatten Sie ein Schwächegefühl auf einer Körperseite?	1	2	3	4
41. Bereitete es Ihnen Mühe, die richtigen Worte zu finden, um sich auszudrücken?	1	2	3	4
42. Hatten Sie Schwierigkeiten beim Sprechen?	1	2	3	4
43. Bereitete es Ihnen Mühe, anderen Ihre Gedanken mitzuteilen?	1	2	3	4
44. Fühlten Sie sich tagsüber schläfrig?	1	2	3	4
45. Hatten Sie Koordinationsprobleme?	1	2	3	4
46. Machte Ihnen Haarverlust zu schaffen?	1	2	3	4
47. Machte Ihnen Hautjucken zu schaffen?	1	2	3	4
48. Hatten Sie Schwächegefühle in beiden Beinen?	1	2	3	4
49. Fühlten Sie sich unsicher auf den Beinen?	1	2	3	4
50. Hatten Sie Mühe, Ihre Blase zu kontrollieren?	1	2	3	4