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TITLE: A single arm phase 2 study of the dual mTORC1/mTORC2 inhibitor AZD2014 provided on an intermittent schedule for neurofibromatosis 2 patients with progressive or symptomatic meningiomas

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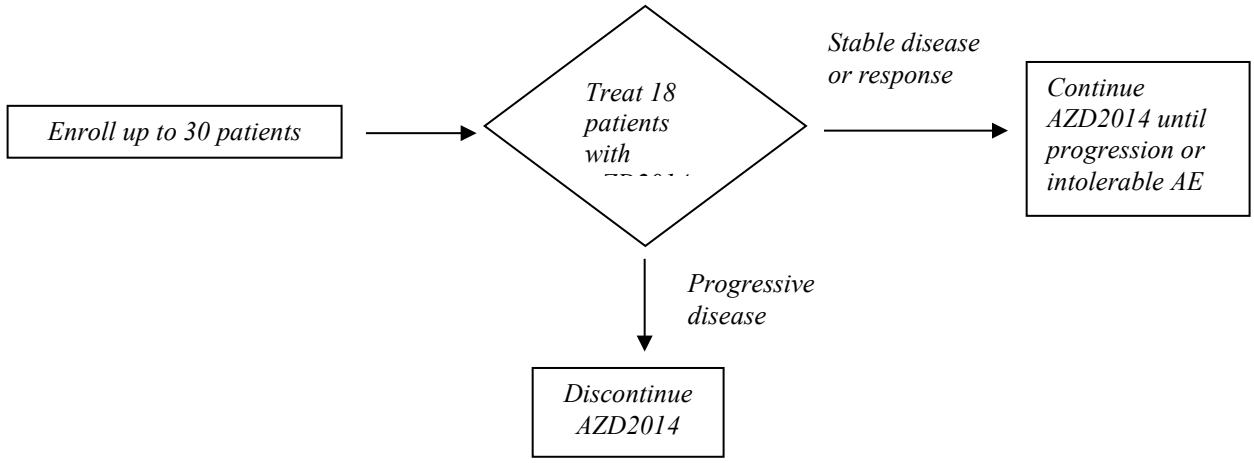
SCHEMA

Phase II trial



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1. OBJECTIVES

The primary hypothesis is that dual mTORC1/2 inhibition with AZD2014 in neurofibromatosis 2 (NF2) patients with progressive or symptomatic meningioma will result in a radiographic response rate greater than historical benchmark of 1%.

The primary objective of this study is to assess whether there is adequate anti-tumor activity of AZD2014 NF2 patients with progressive or symptomatic meningioma to pursue further testing.

The secondary objectives of this study are (1) to correlate genetic and molecular features of previously resected patient tumors with responsiveness to AZD2014, in an effort to identify specific subpopulations of meningioma patients who may respond best to AZD2014, (2) to determine the safety and tolerability of AZD2014 in this patient population, (3) to determine the radiographic response rate of vestibular schwannomas (VS) and (4) to explore changes in quality of life (QoL) during treatment .

1.1 Study Design

This is a single-arm, single-center, open label, phase II study to evaluate the efficacy, safety, and tolerability of AZD2014 in NF2 patients with progressive or symptomatic meningiomas. Up to 30 patients will be enrolled (i.e., consented) in this study in a single stage in order to treat a maximum of 18 patients with AZD2014.

AZD2014 will be administered at a dose of 125 mg (two 50mg tablets and one 25mg tablet) orally twice per day on 2 consecutive days out of every 7 days. One cycle will consist of 28 days (1 cycle = 28 days). Dose reductions or delays will be allowed, if toxicity is observed, as specified in section 6.1. AZD2014 will be administered continuously until criteria for taking a participant off protocol therapy are met, as specified in section 5.6.

Disease evaluation by gadolinium-enhanced magnetic resonance imaging (Gd-MRI) of the brain will occur ≤ 28 days prior to first AZD2014 administration and then after every 3 treatment cycles (i.e., every 12 ± 1 week) up to End of Treatment visit. Tumor assessment will be evaluated by the Tumor Imaging Metrics Core (TIMC) at Massachusetts General Hospital (MGH) using volumetric MRI analysis (see Section 11). Genetic and immunohistochemical analysis of tumor specimens will be performed as a laboratory correlative study. Either 5 unstained slides or a formalin fixed paraffin embedded (FFPE) tumor block sufficient to generate at least 5 unstained slides will be required for each patient as explained in section 9. Frozen tissue tumor blocks will be collected as available.

Patients will be closely monitored for adverse events on an ongoing basis as outlined in section 7. Patients experiencing acute AZD2014-related adverse events may have the AZD2014 study drug delayed until recovery and the dose modified as specified in section 6. If a toxicity persists and AZD2014 is held for > 19 days according to section 6.1, the patient will be removed from the study. Patients will continue to be regularly monitored for safety until 30 days following the last administration of study drug or until the End of Treatment visit, whichever is later. Patients may be withdrawn from the study treatment for unacceptable adverse events despite dose reductions and delays or for disease progression.

1.2 Primary Objectives

The primary objective of this study is to determine the proportion of subjects with a radiographic response in the target meningiomas after treatment with AZD2014.

1.3 Secondary Objectives

The secondary objectives of this study are to correlate the anti-tumor response of AZD2014 on tumors with their genetic and molecular characteristics (when available) to determine the safety and tolerability of AZD2014 in this patient population, to determine the radiographic response rate for vestibular schwannomas, and to explore changes in quality of life (QoL) during treatment. As part of this objective, the following endpoints will be determined:

- Median progression-free survival (PFS)
- Progression-free survival at 6 months (PFS6)
- Duration of radiographic response
- Frequency of adverse events (possibly, probably, or definitely) related to AZD2014 use in this patient population
- Radiographic response rate of vestibular schwannomas (defined as an decrease in VS volume by $\geq$ 20% compared to baseline)
- Proportion of patients with a hearing improvement and decline (response defined as a statistically significant improvement/decline in word recognition score compared with baseline score, Appendix G)
- QoL, as measured by the Neurofibromatosis 2 Impact on Quality of Life (NFTI-QOL) and Penn Acoustic Neuroma-Quality of Life (PAN-QOL) questionnaires
- Clinical outcomes stratified by genetic and immunohistochemical analysis

2. BACKGROUND

2.1 Neurofibromatosis 2

Neurofibromatosis 2 (NF2) is a neurogenetic tumor suppressor syndrome with a birth prevalence of 1 in 25,000[1]. Patients with NF2 have increased risk of multiple tumor types, including schwannomas, meningiomas, and ependymomas[2]. Bilateral VSs are the hallmark of NF2. As these tumors enlarge, they cause sensorineural hearing loss and, ultimately, complete hearing loss. There are two forms of hearing loss in patients with NF2. Gradual hearing loss is the rule, and it most commonly occurs with progression of tumor size over time. Although there is a rough correlation with tumor size, gradual hearing loss can occur with tumors of any size. Although surgical implantation of cochlear and auditory brainstem implants provides benefit for a small minority of patients, there is no widely effective treatment for this type of hearing loss. In addition, some patients can experience episodes of sudden hearing loss superimposed on baseline hearing dysfunction. Treatment with a short course of corticosteroids can often correct this acute hearing loss. The mechanism of acute hearing loss is not clearly understood but probably involves compression of the auditory nerve from tumor mass and associated edema.

2.2 Meningioma

Meningiomas are the second most common tumor in NF2 patients with a cumulative prevalence of 80%

by age 70[3]. In a large series of 74 patients from France, the median number of meningiomas per patient was 3. During a mean follow up of 110 months, 33% of tumors demonstrated significant growth (> 1mm/year). In a subset of tumors with volumetric MRI analysis, 7.3% of meningiomas demonstrated volumetric growth of ≥ 20% per year. Surgery was performed in 46% of patients, most commonly for neurologic symptoms.

The current standard of care for meningioma therapy is maximal safe surgical resection with adjuvant radiation reserved for recurrent tumors or those with aggressive features (e.g. WHO grades II or III). Many systemic therapies have been studied to treat recurrent or progressive meningiomas, though none have demonstrated clinical benefit to date for sporadic of NF2-related meningioma. Based on the female predominance of meningiomas, as well as the high prevalence of progesterone (70%) and estrogen (30%) receptors on meningiomas,[4] hormonal therapies were once a prominent focus of therapeutic trials. However, treatment with the oral progesterone agonist megestrol acetate (megace),[5] the progesterone antagonist mifepristone (RU-486),[6] and the estrogen receptor antagonist tamoxifen[7] has not improved clinical outcomes. Other attempts using more traditional chemotherapies such as temozolomide,[8] irinotecan,[9] and hydroxyurea[10-12] also did not definitively extend patient survival. Trials using biologically targeted approaches with imatinib (anti-PDGFR and c-KIT),[13] erlotinib (anti-EGFR),[14] and gefitinib (anti-EGFR),[14]were also negative. A small phase 2 study of sunitinib (anti-EGFR and PDGFR) for recurrent grade II and III meningioma demonstrated a 6-month progression-free survival of 42% and the authors have recommended a randomized phase 2 study of this drug.[15] Finally, based on the mTOR signaling work produced in this lab, a study of everolimus (anti-mTORC1) has thus far demonstrated cytostatic effect on meningiomas.[16] Therefore, effective medical therapies are greatly needed for these tumors.

2.3 Mammalian Target of Rapamycin (mTOR) signaling in meningioma

Mammalian Target of Rapamyin (mTOR) is an evolutionarily conserved serine/threonine kinase that regulates cell growth, proliferation and survival through two distinct functional complexes, mTORC1 and mTORC2.[17,18] Rapamycin and its analogs (rapalogs) such as RAD001, which efficiently inhibit mTORC1 have been effective in treating tuberous sclerosis complex (TSC) patients,[19] however rapalogs have shown only moderate success in other tumors with mTOR activation. This is probably due to the fact that rapalogs effectively inhibit S6K phosphorylation, but not 4EBP1 phosphorylation, and therefore incompletely inhibit mTORC1-dependent protein synthesis.[20] Rapalogs also do not inhibit mTORC2.[21] Another major concern is that rapalogs cause activation of prosurvival and oncogenic pathways such as PI3K/Akt and MAPK/ERK.

These issues have fueled the development of next generation mTOR kinase inhibitors.[22,23] In our recent studies, we observed that the ATP-competitive mTOR kinase inhibitor Torin1 was more effective in blocking activation of mTORC1 and Akt as well as inhibiting cell proliferation in NF2-deficient meningioma cells compared with rapamycin.[24] Further we have detected specific activation of the mTORC2-dependent AGC kinase SGK1 (serum and glucocorticoid-regulated kinase 1) in primary human meningioma cells with and without NF2 loss. These data are consistent with 1) the elevated *SGK1* transcriptional expression that we observe in cultured arachnoidal cells where NF2 has been deleted *in vitro* and 2) elevated SGK1 protein expression in both NF2-deleted arachnoidal cells and primary human meningioma cells (see Preliminary Results). These observations led us to test dual mTORC1/mTORC2 inhibitor, AZD2014 (kindly provided by AstraZeneca), in our primary human meningioma cells. Our preliminary data convincingly show that activation of mTORC2-dependent

SGK1 in human meningioma cells is sensitive to AZD2014, but insensitive to rapamycin. AZD2014 treatment of primary meningiomas, whether NF2-deficient or NF2-expressing, leads to decreased cell proliferation and shows greater efficacy than rapamycin.

2.4 AZD2014

Mechanism of action
AZD2014 is an inhibitor of the kinase activity of mammalian Target Of Rapamycin (mTOR). mTOR is a serine/threonine kinase belonging to the PI3K (PIKK) superfamily of kinases. AZD2014 is specific for mTOR and does not inhibit other members of the PI3K superfamily. The PI3K-AKT-mTOR pathway functions as a sensor of mitogen, energy and nutrient levels and is a central controller of cell growth. The mTOR is a protein kinase (PK) and a vital component of the PI3K/Akt/mTOR signaling pathway. This pathway is deregulated in 50% of all human cancers and, as such, is an important target for inhibitors that would alleviate the unregulated proliferation of cancer cells.[25]

Rapamycin and its analogs (rapalogs) are potent inhibitors of mTORC1 and have been shown to be clinically effective in certain cancer types like endometrial cancer, mantle cell lymphoma, RCC and breast cancer.[26-28]

Nevertheless, so far, several resistance mechanisms have been shown to limit the response rate in clinical studies to rapamycin and analogues. mTOR exists as two complexes, mTORC1 and mTORC2, defined by their associated proteins, and having different cellular functions. Rapalogs, due to their allosteric mode of interaction with mTOR, inhibit mainly mTORC1, leaving mTORC2 unregulated. There is also evidence that inhibition of only mTORC1 sets off a negative feedback mechanism that leads to increased Akt signaling. The elevation in pAKT may at least in part explain the disappointing results with the rapamycin derivatives in many solid tumors and activation of this feedback loop is associated with a shorter time to progression in phosphatase and tensin homolog deleted on chromosome ten (PTEN) null glioblastoma patients treated with rapamycin.[29]

AZD2014 is selective inhibitor of mTOR kinases and inhibits signaling of both mTOR complexes, mTORC1 and mTORC2. AZD2014 is thereby molecularly different from rapalogues:

- AZD2014 achieves more profound mTORC1 inhibition, in particular inhibiting phosphorylation 4EBP1 and S6
- AZD2014, unlike the rapalogues, also inhibits mTORC2, leading to reduced phosphorylation of AKT.
- AZD2014 has a broader range of growth inhibitory activity *in vitro* across tumor types compared to rapalogues. AZD2014 is especially effective in estrogen receptor (ER)+ breast cancer cell lines and in *in-vivo* sensitive and resistant models to endocrine therapy.

As such, ATP-competitive dual TORC1/TORC2 inhibitors, like AZD2014 that inhibit both mTOR complexes may offer therapeutic advantages to rapalogs.[28]

Key efficacy studies

In the monotherapy study (D2270C00001) at the 50 mg BID dose in a total of 40 patients, 2 patients had an objective response; 1 patient with pancreatic acinar cell type cancer and 1 patient with ER+ breast

cancer had partial responses (PR) according to Response Evaluation Criteria In Solid Tumors (RECIST) and received AZD2014 treatment for 175 and 206 days, respectively. In addition, stable disease has been observed in four patients for more than 100 days. Two breast cancer patients; one ER+ patient and one human epidermal growth factor receptor 2 positive (HER2+) patient were treated with AZD2014 for 141 days and 177 days, respectively. Two patients with endometrioid cancers remained stable for 274 and 333 days, respectively.

Pharmacokinetics
The key findings from the preliminary single-dose and multiple-dose pharmacokinetic (PK) data are summarized below (for details and discussion see Investigator Brochure section 5.1):

- AZD2014 is orally available and rapidly absorbed when administered as a tablet (median t_{max} for solution = 0.25 to 1.5 h across 25mg to 125mg dose range).
- AZD2014 has a short terminal elimination half-life with high inter-patient variability (mean $t_{½}$ following single solution dose approximately 3.3 h, range 0.9 – 9.1 h, across the 25mg to 125mg dose range).
- AZD2014 exposure increases greater than proportionally to dose (5-fold increase in single solution dose from 25 to 125 mg gives on average approximately a 13-fold increase in AUC and 9-fold increase in C_{max}).
- AZD2014 has high inter-patient variability in exposure within each dose level with overlapping individual exposures across the dose levels (CV=75% and 48% for AUC_{ss} and $Cmax_{ss}$ respectively at 50mg BD tablet dose in Study D2270C00001).
- AZD2014 has a low apparent Volume of Distribution but adverse events and biomarker modulation suggest the compound distributes to tissues.
- AZD2014 has low apparent clearance from the body that decreases following multiple dosing ($CL_{ss}/F < CL/F$ for the same dose; Fraction of dose (F) absorbed not known).
- AZD2014 single dose PK data are not predictive of the steady state kinetics in many patients, with greater than expected accumulation (mean R_{AC} range 1.6 – 2.6 across the continuously dosed cohorts compared with the average of just over 1 predicted from single dose data; individual range from 0.61 to 9.5) and greater temporal change values than the average of 1.0 expected if there were no time dependent effects (mean T_C mean range 1.5 to 2.4 across the continuously dosed cohorts; individual range from 0.59 to 9.4).
- There is no evidence that a clinically relevant drug interaction between AZD2014 and fulvestrant is likely (range of AZD2014 exposures achieved following continuous multiple dosing of the tablet in combination with fulvestrant in Study D2270C00005 is similar to that in monotherapy in Study D2270C00001).
- AZD2014 tablet PK data from the intermittent weekly (BD 2/5) dosed schedules (100 – 225mg BD for 2 days followed by a 5 day wash-out period) show that:
    - High AZD2014 doses are more slowly absorbed than lower doses (median t_{max} following last weekly dose [LWD] 1.5 – 2h)
    - Terminal elimination half life is much longer following multiple and high tablet doses than that seen following single and lower tablet doses (mean $t_{1/2}$ following the LWD of

intermittent schedules = 5.1 to 9.4 h compared with mean $t_{1/2}$ of 2.8 – 6.3 h across the 35mg to 175mg single tablet dose range)
    - Accumulation of drug is higher in the intermittent dose schedules than for the lower tablet doses given in the continuously dosed BD and QD cohorts (mean R_{AC} range 2.2 – 5.0 for intermittent schedules compared with 2.1 to 2.6 for 35-50mg BD tablet cohorts
    - Using the intermittent dose schedules similar weekly AZD2014 exposures (AUC) can be achieved to those from a similar weekly dose given as a continuous lower dose daily schedule with much higher peak concentrations being achieved over the first few days of the week.
- Administering AZD2014 with food appears to delay absorption and reduce the peak systemic exposure. Based on a randomized within patient single dose comparison in Study D2270C00001 (n=18), using the 50 mg tablet formulation administered under fed (standard meal) and fasted (3 h) conditions. On average C_{max} was lower in the fed state (644 ng/mL vs. 856 ng/mL fasted) and t_{max} delayed (3 h vs. 1 h fasted). A mixed-effects analysis estimated the AUC (fed/fasted) ratio as 0.95 (0.84 for sensitivity analysis set) with 90% confidence intervals 0.71–1.27 (0.68–1.03 for sensitivity set), indicating no effect on AUC. In addition, results of a combined population PK analysis of both studies support the conclusion that there was no effect of a standard meal on AUC.
- While there is a clear relationship between dose and tolerability, with fewer patients tolerating the dose and more showing dose limiting toxicities as the level increases, there is no clear relationship yet established between exposure [PK] and safety or efficacy endpoints [PD].

Pharmacodynamics

- At a dose of 50 mg BD, AZD2014 reduced cytoplasmic pS6 (S235/236) IHC staining in 8 out of 8 tumor biopsies obtained after 1 to 5 hours of therapy indicating that the drug has mTORC1 activity. Phosphorylation of 4E-BP1 (T37/46) was decreased post treatment in 3 out of 4 evaluable paired biopsies obtained after 1 to 5 hours of therapy.
- In monocytes, the median % change in p4E-BP1 at 2 hours after a single dose of AZD2014 was -45.7% (n = 19 range -96.9% to +37.3%) at 50 mg BD and -48.3% (n = 2 range -87.7% to -8.9%) at 125 mg intermittent weekly dosing schedule (2 days on, 5 days off). By 6 to 8 hours, the median % change in p4E-BP1 was - 45.9% (n = 18, range -93.9% to +32.7%) at 50 mg BD and -11.7% (n = 2, range -50.1% to +26.8%) at 125 mg intermittent weekly dosing schedule in D2270C00001. Phosphorylation of 4E-BP1 was also reduced following treatment at the lower dose of 100 mg on the intermittent weekly dosing schedule in study D2270C00001.
- Phosphorylation of AKT (S473) was inhibited in platelet rich plasma (PRP) providing evidence for TORC2 inhibition in surrogate tissue. At 2 hours after a single dose of AZD2014 the median % change was -62.5% (n = 43 range -98.7% to +13.5%) at 50 mg BD and -63.4% (n = 5 range -92.1% to -7.0%) at 125 mg intermittent weekly dosing schedule in D2270C00001. By 6 to 8 hours, the median % change was -43.6% (n = 45 range –93.1% to +62.7%) at 50 mg BD and -34.7% (n = 5 range -83.1% to +7.4%) at 125 mg intermittent weekly dosing schedule. Phosphorylation of AKT was also reduced following treatment at the lower doses of 25 mg BD, 35mg BD and 100 mg on the intermittent weekly dosing schedule.

There was no evidence for an elevation in cytoplasmic pAKT (S473) (mTORC2 phosphorylation site) in

tumor biopsies indicating that AZD2014 may be differentiated from everolimus which has been reported to increase phosphorylation on this site in approximately 50% of cases. In tumor biopsies, phosphorylation of AKT (S473) was lower in the post-treatment biopsies in 3 out of 4 evaluable samples obtained after 1 to 5 hours of therapy. A lower level of pAKT (T308) was also observed after treatment in 3 out of 6 tumor biopsies taken 1 to 5 hours after dosing.

Dosing

As of cut-off date of December 31, 2014, 343 patients have been enrolled in studies with AZD2014; 211 in AZ-sponsored studies, and 132 in externally sponsored research (ESCR) studies. A total of 301 patients have received AZD2014; 211 in AZ-sponsored studies, and approximately 90 in ESCR studies. Two AstraZeneca-sponsored Phase 1 studies were designed to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of AZD2014: D2270C00001 (monotherapy); and D2270C00005 (in combination with fulvestrant). Data collection for study D2270C00001 is now complete and reporting activities are ongoing, whilst study D2270C00005 is ongoing.

Several doses and dosing schedules of AZD2014 have been explored in both the monotherapy (D2270C00001) and combination (D2270C00005) studies:

AZD2014 Monotherapy (D2270C00001):

Table 1:

Dosing schedule	Doses explored	Defined MTD
Intermittent weekly BID dosing (2 consecutive days, 2 days on, 5 days off)	100 mg, 125 mg 170 mg, 225 mg	125 mg (2 consecutive days, 2 days on, 5 days off)
Continuous BID dosing	25 mg, 50 mg, 70 mg, 100 mg	50 mg
Continuous QD dosing	75 mg, 100 mg, 125 mg, 175 mg	100 mg

BID – twice daily dosing, QD- once daily dosing, MTD – maximum tolerated dose

AZD2014 is available for administration as a tablet for use in clinical studies and is presented as three strengths: 10, 25 or 50 mg. The intermittent dosing schedule (2 consecutive days, 2 days on, 5 days off) has an improved safety profile compared to the continuous dosing schedule and as a result, the intermittent schedule (2 consecutive days, 2 days on 5 days off), will now be prioritized for use in all new AZD2014 studies. Details of all AZD2014 studies, including 5 ESCRs, are summarized in Table 2 and Table 4 in Section 5 of the IB edition 5.

Safety profile

Overall, the safety profile of AZD2014 is consistent with other mTOR inhibitors and the incidence and severity of individual toxicities such as rash, mucositis and hyperglycemia can be improved by the use of intermittent (2 consecutive days, 2 days on, 5 days off) rather than continuous dosing.

In Study D2270C00001, 86.7 % of patients experienced at least 1 adverse event (AE) considered related to AZD2014 by the reporting investigator. The most common AEs related to study treatment (occurring in ≥15 % patients overall across all cohorts) were fatigue (58.5 %), nausea (48.1 %), mucositis (29.6 %), diarrhea (28.1 %), rash (27.4 %), decreased appetite (22.2 %), vomiting (21.5 %) and hyperglycemia (15.6 %). Dose limiting toxicities (DLTs) reported at non-tolerated doses were fatigue, diarrhea, mucositis, nausea, vomiting and rash. During the study, 55/135 (40.7 %) patients had a serious adverse event (SAE), and 24/135 (17.8 %) had a treatment-related SAE. One patient died due to an AE of

pulmonary embolism during the study; this was deemed unrelated to treatment by the investigator. 26 patients (19.3 %) reported at least 1 AE leading to discontinuation. The most common AEs leading to discontinuation of AZD2014 (reported in ≥4 patients overall) were fatigue (7.4 %), nausea (4.4 %), decreased appetite (3.0 %), diarrhea (3.0 %), mucositis (3.0 %), rash (3.0 %), and vomiting (3.0 %).

Although most patients experienced an AE, the drug was considered to be well tolerated with easily manageable side effects by the investigators. A total of 68 patients (50.4 %) experienced an AE of Common Terminology Criteria for Adverse Events (CTCAE) grade 3, 1 patient (1.3 %) had a CTCAE grade 4 AE, and 1 patient (1.3 %) had a CTCAE grade 5 AE (incidence rates include DLTs at non-tolerated doses). 15 (12 %) patients on doses below the MTD experienced AEs that led to the discontinuation of AZD2014 and no patients on a dose below the MTD for the QD continuous and intermittent (2 consecutive days, 2 days on, 5 days off) dosing schedules reported any AEs which led to discontinuation. AEs that defined the drug's non-tolerability were generally reversible within a week of stopping treatment with AZD2014. 105 patients (77.8 %) had a duration of treatment (including periods of dose interruption) of >3 months. 1 patient had duration of treatment of 18 months.

The change from the continuous dosing at a dose of 50 mg BID to the intermittent (2 consecutive days, 2 days on, 5 days off) dosing of AZD2014 at a dose of 125 mg BID was accompanied by an increase in the incidence of nausea (from 20/41 [48.8 %] to 9/13 [69.2 %]) and diarrhea (from 18/41 [44.0 %] to 9/13 [69.2 %]), however, it reduced the incidence of rash (from 20/41 [48.8 %] to 2/13 [15.4 %]) and mucositis (from 18/41 [43.9 %] to 4/13 [30.8 %]) . The 125 mg 2 consecutive days, 2 days on, 5 days off schedule did not have any AE's associated with discontinuation with AZD2014, compared to the continuous 50 mg BD schedule, for which 18/41(43.9 %) patients discontinued treatment as a result of an AE.

Cardiac issues
Overall, no clinically significant changes were observed in heart rate or blood pressure. Single intermittent systolic or diastolic blood pressure values above and below normal values were reported in a few patients. Intermittent higher heart rates >100 bpm were observed, and tachycardia was reported as an AE in 7 patients, of which 1 was serious (See Investigator Brochure Section 5.2.4). A confounding factor in most of these patients was concurrent anemia related to their underlying disease.

ECG changes
In pre-clinical Safety Pharmacology studies, increases in heart rate, blood pressure, myocardial contractility, coronary flow and minor QTc prolongation were observed. Study D2270C00001 (study 1) and Study D2270C00005 (study 5) were therefore designed with appropriate monitoring including triplicate ECG assessments at screening, during the studies, at study drug discontinuation, and at the 30-day follow-up visit. MuGA or echocardiography was performed at screening, at discontinuation and during the study when clinically indicated.

As of Dec 02, 2013 over 155 patients received at least one dose of AZD2014 in Study D2270C00001 and Study D2270C00005. All ECGs were reviewed centrally by a contract vendor. Repolarization abnormalities (T wave flattening and or T wave inversion) were identified in 11 patients, 8 from study D2270C00001 and 3 patients from study D2270C00005. All ECGs repolarization changes from first 54 patients in study D2270C00001 were reviewed by an independent external cardiologist, who identified ECG repolarization changes comprising progressive T-wave flattening in 4 of the 54 patients. In 3 of those patients who continued on treatment, the flattening progressed to T-wave inversion. These findings

occurred slowly, starting from minimal T-wave flattening to inversions over several weeks, stayed at negative values for several weeks and returned back to low/normal over a period of weeks while on treatment. The patients with these findings showed no clinical signs and symptoms of compromised cardiac function or any elevations in cardiac enzymes. Thirty-day follow-up ECGs were available for 2 patients. ECGs of one patient returned back to normal values and ECGs of another patient the limb leads were very similar to baseline but the chest leads stayed generally smaller in amplitude and remained inverted in V2 and V3.

In the monotherapy trial, study D2270C00001, another 4 patients developed similar findings, including T-wave flattenings without inversions (except 1 patient, who showed both, flattening and inversions). The patient with both findings, experienced recovery from both Twave abnormalities while on treatment. For the 3 other patients, the T-wave flattening occurred irregularly during the treatment periods with intermittent normal ECGs, however, resolved completely after stopping the drug permanently. In the combination trial, (Study D2270C00005) T-wave flattenings were observed in 3 patients intermittently and resolved while on treatment. None of these 11 patients showed any cardiac signs or symptoms at the time of the ECG changes and 1 of these patients has had continuous electrolyte imbalances, which may have contributed to the findings.

The external cardiologist's opinion regarding these changes is as follows:

- There are no significant QRS morphology changes during the trial
- Repolarization changes are therefore primary rather than secondary to a change in depolarization
- These 4 patients showed stereotyped progressive repolarization abnormalities with T wave flattening and inversion most marked in the lateral chest leads
- The mechanism of these changes is unknown
    - Their progressive development over weeks is not compatible with an ischemic insult
    - their variable onset and progression suggests that on-going screening during dosing is required
    - Their reduction during on-going drug therapy is not compatible with a purely dose dependent phenomenon
    - No risk factor for the development of these repolarization changes has been identified
    - As T wave morphology is thought to be determined by differential depolarization across the myocardial wall, in vitro study may be helpful although inter-species differences may hinder interpretation
- The clinical significance of these changes is also unknown although no clinical events related to left ventricular function or arrhythmia have been recorded.

Medical assessment by AstraZeneca of ECG changes in the latest 7an additional 32 patients in August 2014 patients is in line with the independent external cardiologist's opinion as described above.

Left ventricular ejection fraction (LVEF)

Of patients who underwent echocardiogram to estimate left ventricular ejection fraction, there were no significant changes in LVEF measurements across all patients. All values in patients who underwent multi-gated acquisition (MuGA) scans were within the normal range for the institution.

Laboratory abnormalities

Review of emerging laboratory data revealed clinically significant changes in transaminases, alkaline phosphatase or bilirubin considered related to AZD2014. Transaminase increases (ALT or AST) were

reported as AEs in 12 patients, the majority were CTCAE Grade 1 and were not considered related to AZD2014 by the reporting investigator. Commonly these events were reported in patients with liver metastases. There were no reports of potential Hy's Law or drug induced liver injury. Hepatic related AEs were reported in 3 of the 4 patients, with 1 patient's events, which included biliary sepsis, considered related to AZD2014 by the reporting Investigator. Reductions in phosphate and potassium have been noted and are discussed in OAEs (See Investigator Brochure Section 5.2.5).

Anemia was reported as an AE in 28 (22.6%) patients overall, and 13 (25.5%) of patients in Part B expansion at 50 mg BD. In the Part B expansion, with the exception of one Grade 3 event of anemia the remainder were all Grade 1-2. Review of laboratory data in Part A at doses up to 100 mg BD revealed the following reductions; lymphocytes grade 1-3 (54%), leukocytes (21%) mainly Grade 1, platelets (15 %) mainly Grade 1, neutrophils (15%) Grade 1-2. Other than anemia, hematology related AEs reported in Part A were three Grade 1 reports of thrombocytopenia, two Grade 1 reports of leukopenia and 3 Grade 1-2 reports of neutropenia. Other than anemia, the only other hematology related AEs reported in study Part B have been thrombocytopenia in 2 patients (both Grade 1). Laboratory data suggests that for most patients who do have reductions in cell counts, values return to patients' baseline on stopping AZD2014. The clinical relevance of these changes appears low given that there was no excess of related AEs such as infection, fungal disease, viral disease, dyspnea, or bleeding within these patients when compared with patients not noted as having reductions in these parameters, and there were no events of greater severity.

The AEs that led to interruption or a dose reduction were generally events known to be associated with AZD2014, such as fatigue, mucositis, rash and gastrointestinal symptoms at higher doses.

Mucositis
Mucositis was amongst the most common AEs reported with a single dose of AZD2014, and at doses of 70 mg BD and 100 mg BD monotherapy was amongst those events considered as dose-limiting toxicities (DLT). Mucositis is generally reversible with AEs improving in severity or resolving completely after AZD2014 is stopped or dose reduced (within 1 day to 1 week).

In study D2270C00001 Part B expansion at 50 mg BD, 19 (37.3%) patients were reported to have experienced mucositis. In study D2270C00005 Part A at all doses, 26 (57.8%) patients experienced mucositis. The majority of events are Grade 1, and there was only 1 report of Grade 3 mucositis in 51 patients in the Study D2270C00001 Part B expansion at 50 mg BD. Incidence of mucositis was relatively lower in the intermittent cohorts.

Fatigue or lethargy
Fatigue was amongst the most common AEs reported with a single dose of AZD2014, and at doses of 70 mg BD and 100 mg BD monotherapy was amongst those events considered as dose-limiting toxicities (DLT). Fatigue is generally reversible with AEs improving in severity or resolving completely within 1 week after AZD2014 is stopped or dose reduced.

In study D2270C00001 Part B expansion at 50 mg BD, 39 (76.5%) patients were reported to have experienced fatigue. With the exception of 2 (3.9%) patients with Grade 3 fatigue, the remainder were all Grade 1-2. In study D2270C00005 at all doses, 26 (57.8%) patients at all doses experienced fatigue. With the exception of 4 (8.9%) patients with Grade 3 fatigue, the remainder were all Grade 1-2.

Gastrointestinal events
Nausea, vomiting and diarrhea were amongst the most common AEs reported after a single dose of AZD2014 In study D2270C00001 Part B expansion at 50 mg BD., nausea was reported in approximately half of patients, with the majority of events (43%) Grade 1-2, and mainly Grade 1 (35.3%). In study D2270C00005 all doses overall, nausea was reported in approximately half of patients. There were no Grade 3 AEs of nausea reported, and the majority (19 of 23) were Grade 1.

In study D2270C00001 Part B expansion at 50 mg BD, diarrhea was reported in approximately half of patients (47.1%), with the exception of one Grade 3 event, the remainder were Grade 1-2, and mainly Grade 1 (35.3%). Vomiting was reported in 17 (33.3%) patients, with the majority (29.4%) Grade 1-2,and mainly Grade 1 (21.6%). %). In study D2270C00005 all doses overall, diarrhea was reported in 22 (48.9%) patients, with the majority (44.4%) Grade 1-2. Vomiting was reported in 11 (24.4%) patients, with the majority (20%) Grade 1-2.

The AEs improved in severity or resolved completely within 1 day after the drug was stopped or dose reduced.

Rash
In study D2270C00001 Part B expansion at 50 mg BD, 24 (47.1%) patients experienced rash of any type. The majority (39.2) were Grade 1.

In study D2270C00005 all doses overall, 27 (60.0%) of 45 patients at all doses experienced rash. Twelve patients (26.7%) experienced CTCAE Grade 1, 7 (15.6%) were CTCAE Grade 2, and 8 (17.8%) of patients experienced CTCAE Grade 3 rash. In study D2270C00005 69% of patients experienced rash on the 50mg BD continuous dosing schedule versus 20% on the 125mg BD intermittent schedule. In study D2270C00001 49% of patients experienced rash on the 50mg BD continuous dosing schedule versus 15% on the 125mg BD intermittent schedule

There was no clear pattern in the type of rash reported which included erythematous, maculopapular and pruritic.

Glucose metabolism
Emerging laboratory data suggest a trend towards increase in blood glucose over time. Insulin and blood glucose elevations have been observed in both monotherapy and in combination therapy studies, a finding frequently described with other mTOR inhibitors as well.

As of 31st Dec 2014, 22.2 % of patients in study D2270C00001 and 5-14.5% of patients in study D2270C00005had hyperglycemia. Overall, in studies D2270C00001 and D2270C00005 hyperglycemia has been reported in approximately 10% of patients. There was 1 reported AE of diabetes mellitus in Study D2270C00005.

There have been reports of SAEs of hyperglycemia reported with AZD2014, including patients requiring in patient hospitalization and treatment with insulin to achieve glycemic control. A patient receiving AZD2014 225mg BD intermittent weekly schedule monotherapy developed grade 3 hyperglycemia, requiring hospitalization and has to be treated with insulin to achieve glycemic control and this was declared a DLT.

Pneumonitis and interstitial lung disease
In Study D2270C00001 Part B expansion at 50 mg BD, 1 patient of 51 (2%) was reported with pneumonitis (Grade 2). Other respiratory events have been reported as follows: 11 reports of respiratory infection events (21.5%) (influenza like illness, nasopharyngitis, lower respiratory tract infection etc.), cough 10 (19.6%) patients, dyspnea 7 (13.7), dyspnea exertional 6 (11.8%), pneumonitis 1 (2.0%), productive cough 1 (2.0%), wheezing 1 (2.0%) patient.

In Study D2270C00005 overall at all doses, in 45 patients, 3 patients (6.7%) were reported with pneumonitis (Grade 1-2). Other than 10 respiratory infection events (bronchitis, influenza, sinusitis etc.), the following respiratory AEs were reported: dyspnea exertional 7 (15.6%), cough 6 (13.3%), bronchitis 3 (6.7%), breath sounds abnormal 2 (4.4%), productive cough 2 (4.4%), dyspnea 1 (2.2%), acute respiratory failure 1 (2.2%), wheezing 1 (2.2%).

Overall Safety conclusions
According to the Investigator's Brochure, although the incidence rate of some AEs seems to be common to frequent, AZD2014 is considered to be generally well tolerated with most of the AEs classified as CTCAE grade 1 and 2, AEs disappeared quickly after short periods of dose interruptions, which allowed patients to stay on the drug for long periods of time (over 1 year). Fatigue, mucositis, rash, nausea, vomiting, diarrhea, hyperglycemia and decreased appetite were the AEs consistently amongst the most frequently reported overall, and those reported as related to AZD2014 by the investigators. These AEs were also those reported with the highest severity grade and were those AEs most commonly leading to dose interruption and/or permanent discontinuation of AZD2014. These events were generally reversible within 1 week by cessation of AZD2014. Interestingly, the AE profile of continuous and intermittent dosing schedules varied slightly. Gastrointestinal events were observed more frequently in the intermittent schedules whereas no occurrence of rash and hyperglycemia has been reported so far for the intermittent dosing schedules.

Potential Drug-drug interactions between AZD2014 and other drugs

Cytochrome P450 and transporter related inhibition and induction:
CYP3A5 and CYP3A4 have been identified *in vitro* as the principal P450s responsible for human metabolism of AZD2014, indicating the possibility of drug-drug interactions with inhibitors and inducers of these enzymes. AZD2014 has also been identified *in vitro* as a substrate for the drug transporters Pgp (MDR1) and BCRP. Co-administration of CYP3A4, CYP3A5, Pgp (MDR1) or BCRP inhibitors may increase exposure to AZD2014 and increase the likelihood of toxicity. In addition, co-administration of CYP3A4 or CYP3A5 inducers may decrease the exposure to AZD2014 and hence potentially affect efficacy.

AZD2014 is a weak inhibitor of multiple P450 enzymes in vitro, including CYPs 2D6, 2C8, 2C9 and 2C19 and MDR1 (PgP) and BCRP transporters, respectively. Clinical drug interaction studies with appropriate substrate probes have not been conducted. However, results of computer simulations using the validated proprietory software SIMCYP™ (Certara Inc., Ca), using the intermittent monotherapy MTD regimen, 125 mg BID, 2 days on 5 days off, demonstrates a clinically relevant PK drug interaction with sensitive substrates of these P450 enzymes and transporters is unlikely (validated probe drugs used: 2D6 dextromethorphan, 2C8 – repaglinide, 2C9 – warfarin, 2C19 – omeprazole, MDR1 – digoxin, BCRP – pravastatin).

The possibility that AZD2014 may precipitate drug interactions due to inhibition of the drug transporters OATP1B1, OATP1B3, OCT1 and OCT2 cannot be excluded. Co-administration of AZD2014, particularly at high doses, with known or possible substrates of these transporters may lead to their increased exposure and requires careful evaluation. The possibility that AZD2014 may precipitate drug interactions due to induction of the drug metabolising enzymes CYP1A2, CYP2B6 or CYP3A4 cannot be excluded. Co-administration of AZD2014, particularly at high doses, with known or possible substrates of these enzymes may lead to their decreased exposure and hence potentially affect efficacy.

Co-medications which are moderate or potent inhibitors of CYP3A4/5, Pgp (MDR1) and BCRP or are sensitive or narrow therapeutic range substrates of the drug transporters OATP1B1, OATP1B3, OCT1 and OCT2 will be restricted and listings of such co-medications are given in Appendix B and the Exclusion Criteria section and other advice provided in the Concomitant Treatments section.

2.5 Rationale

Previous studies from the Ramesh laboratory demonstrated constitutive activation of mammalian/mechanistic target of rapamycin complex 1 (mTORC1) signaling in human meningiomas,[30] leading to ongoing clinical trials with rapalogs for NF2-related meningioma. The laboratory further observed specific activation of pNDRG1, a read out for SGK1, in meningiomas and demonstrated that dual mTOR kinase inhibitor such as Torin 1 is more effective than rapamycin in inhibiting the proliferation of NF2-deficient cells [31]. This work led to an R21 NIH grant to test dual mTORC1 and mTORC2 inhibitor, AZD2014 in *NF2*-null cells (kindly provided by AstraZeneca for this study). In parallel, employing a high throughput shRNA kinome screen, the Ramesh laboratory has recently identified mTORC2-specific AGC kinase, SGK1, as a top candidate kinase activated in *NF2*-deficient human meningioma cells. Our published data convincingly show that activation of SGK1/pNDRG1 in *NF2*-null human cells is sensitive to inhibition by AZD2014, but insensitive to inhibition by rapamycin[32]. Further, we have seen elevated expression of SGK1 in both *NF2*-null and *NF2*-expressing primary meningioma cells. Most importantly, treatment of NF2 patient-derived primary meningioma cells as well as primary meningioma cells from sporadic individuals without NF2 loss using AZD2014 leads to decreased cell viability and shows significantly greater efficacy than rapamycin. These results strongly support that AZD2014 should be considered for a clinical trial for human meningiomas.

2.6 Correlative Studies Background

Chromosome 22 loss and *NF2* mutations are known to occur in all NF2-related meningiomas and in 50-60% of sporadic meningiomas. We propose to perform targeted resequencing of the *NF2* gene in all available target and non-target tumors for patients enrolled in this study. This genetic information will allow us to draw the conclusion whether there is a correlation between response to AZD2014 and genetic variation(s) in the *NF2* gene in meningiomas. In addition, tumor DNA will be stored for future use in genetic studies as approved by local IRB.

Work from the Ramesh laboratory has established the activation of mTORC1 and mTORC2 in NF2-associated meningiomas. Therefore as an additional correlation, we propose to perform immunohistochemistry (IHC) analyses of mTORC1 and mTORC2 signaling for all available archival meningioma samples for patients enrolled in this study.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have a confirmed diagnosis of neurofibromatosis 2 by fulfilling National Institute of Health (NIH) criteria or Manchester criteria, or by detection of a causative mutation in the NF2 gene.

The NIH criteria[33] includes presence of:

- Bilateral vestibular schwannomas, **OR**
- First-degree relative with NF2 and **EITHER** unilateral eighth nerve mass **OR** two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity.

The Manchester criteria[34] includes presence of:

- Bilateral vestibular schwannomas, **OR**
- First-degree relative with NF2 and **EITHER** unilateral eighth nerve mass OR two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, **OR**
- Unilateral vestibular schwannoma **AND** any two of: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, **OR**
- Multiple meningiomas (two or more) **AND** unilateral vestibular schwannoma **OR** any two of: schwannoma, glioma, neurofibroma, cataract.

3.1.2 Participants must have progressive or symptomatic meningioma.

NOTE: Histologic confirmation of target meningioma is not required in the setting of compatible radiographic appearance.
NOTE: progression is defined as an increase in target meningioma volume ≥ 20% **OR** ≥ 3 mm during the past 2 years.

3.1.3 Subjects must have a target meningioma that is not amenable to surgery due to patient preference or high risk for surgical complications

3.1.4 Participants must be willing and able to undergo regular MRI scans of the brain

3.1.5 Patients must have measurable disease, defined as at least one meningioma ≥ 1.0 ml (on volumetric analysis performed by the Tumor Imaging Metric Core at DF/HCC) that can be accurately measured by contrast-enhanced cranial MRI scan, performed within 28 days of study registration.

3.1.6 Prior surgical resection and radiation therapy for the progressive meningioma are not required for study enrollment.

3.1.7 Patients must have received less than 3 prior chemotherapy regimens for progressive meningioma.

3.1.8 Patients must have available an archival paraffin tumor block (from surgery on any meningioma or schwannoma) sufficient to generate at least 5 unstained slides; or, if a paraffin tumor block is unavailable, at least 5 unstained slides. Note: tumor block from the target meningioma is not required.

3.1.9 Age ≥ 18 years at the time of study enrollment.

3.1.10 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A) with no deterioration over the previous 2 weeks.

3.1.11 Life expectancy of greater than 3 months.

3.1.12 Within 14 days of study registration, participants must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– hemoglobin	≥9.0 g/dL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 x institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– Serum creatinine	≤1.5 x institutional upper limit of normal concurrent with creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft and Gault equation), confirmation of creatinine clearance is only required when creatinine is >1.5xULN
– Urine protein	≤1+ on urine dipstick (if 2+ seen on first test, re-test at least 24 hours later)
– PT/INR/PTT (aPTT)	<1.5x institutional upper limit of normal

3.1.13 The effects of AZD2014 on the developing human fetus are unknown. For this reason and because mTOR kinase inhibiting agents are known to be teratogenic, female patients must be willing to use 2 forms of highly effective contraception (per institution standards) from the time of screening until 4 weeks after discontinuing study, must not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child bearing potential or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening: (1) post-menopausal women, defined as either women aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, or, (2) women under 50 years old who have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the postmenopausal range for the institution. Alternatively, women must have documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

Male patients should either be surgically sterile or willing to use an effective barrier method of contraception during the study and for 16 weeks following the last dose of study treatment if sexually active with a female of childbearing potential. If not done previously, storage of sperm prior to receiving AZD2014 will be advised to male patients with a desire to have children.

3.1.14 Ability to understand and the willingness to sign a written informed consent document prior to any study specific procedures, sampling, and analyses.

3.1.15 Ability to swallow and retain oral medication.

3.2 Exclusion Criteria

3.2.1 Prior chemotherapy, biological therapy, radiation therapy, androgens, thalidomide, immunotherapy, other anticancer agents within 21 days of starting study treatment (not including palliative radiotherapy at focal sites). Prior use of an investigational monoclonal antibody therapy within 3 months, or prior use of nitrosoureas or mitomycin C within 6 weeks. Patients must have recovered from acute toxicity due to radiotherapy.

3.2.2 With the exception of alopecia, any unresolved toxicities from prior anti-tumor treatments (excluding corticosteroids) should be no greater than CTCAE (Version 4.0) Grade 1 at the time of study entry.

3.2.3 Major surgery within 4 weeks prior to entry to the study (excluding placement of vascular access), or minor surgery (excluding tumor biopsies) within 14 days of first dose of study treatment.

3.2.4 Participation in another clinical study with an investigational product during the last 21 days.

3.2.5 History of hypersensitivity to active or inactive excipients of AZD2014 or drugs with a similar chemical structure or class to AZD2014.

3.2.6 Exposure to potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP if taken within the stated washout periods before the first dose of study treatment (see Appendix B).

3.2.7 Exposure to sensitive or narrow therapeutic range substrates of the drug metabolising enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 within the appropriate wash-out period (a minimum of 5 x reported elimination half-life) before the first dose of study treatment (see Appendix B).

3.2.8 Any hematopoietic growth factors (e.g., filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostim [granulocyte-macrophage colony-stimulating factor; GM-CSF]) within 14 days prior to receiving study treatment.

3.2.9 Pre-treatment with other mTOR inhibitors may be allowed and should be discussed with the medical monitor.

3.2.10 Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

3.2.11 Previous meningioma progression during treatment with other mTORC1/2 inhibitors (but not mTORC1 inhibitors such as everolimus or other rapalogues).

3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, severe hepatic impairment, interstitial lung disease (bilateral, diffuse, parenchymal lung disease), uncontrolled chronic renal diseases (glomerulonephritis, nephrotic syndrome, Fanconi Syndrome or renal tubular acidosis), current unstable or uncompensated respiratory or cardiac conditions, uncontrolled hypertension, active bleeding diatheses, active hepatitis B or C infection, known active human immunodeficiency virus (HIV) infection, or psychiatric illness/social situations that would limit compliance with study requirements. Screening for chronic conditions is not required.

3.2.13 History of other malignancies, except: Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician, (2) adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, (3) adequately treated carcinoma in situ without evidence of disease, or (4) Gleason 6 prostate cancer under observation.

3.2.14 Patients who have experienced any of the following procedures or conditions currently or in the preceding 12 months:

- coronary artery bypass graft
- angioplasty
- vascular stent
- myocardial infarction
- angina pectoris
- congestive heart failure New York Heart Association Grade ≥2 (ventricular arrhythmias requiring continuous therapy)
- supraventricular arrhythmias including atrial fibrillation, which are uncontrolled
- haemorrhagic or thrombotic stroke, including transient ischaemic attacks or any other central nervous system bleeding
- History of drug abuse or alcohol abuse, as judged by the Investigator

3.2.15 Abnormal echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) at baseline (left ventricular ejection fraction [LVEF] <55%. Appropriate correction to be used if a MUGA is performed.

3.2.16 Pre-existing renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis.

3.2.17 Mean resting corrected QT interval (QTc), calculated using Fridericia's formula, > 470 msec obtained from 3 electrocardiograms (ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes within 12 months of the patient entering in the study.

3.2.18 Patients with uncontrolled Type II (HbA1c >8% assessed locally) as judged by the Investigator or Abnormal fasting glucose value defined as >126 mg/dL (>7 mmol/L).

3.2.19 Concomitant medications known to prolong QT interval, or with factors that increase the risk of QTc prolongation or risk of arrhythmic events (such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age). See appendix B for a list of medications.

3.2.20 Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug.

3.2.21 Judgment by the Investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements. **Note**: patients who are likely to require surgery or radiation for NF2-related tumors during the first year of treatment in the investigator's opinion should not be enrolled on this clinical trial.

3.2.22 Pregnant women are excluded from this study because AZD2014 is an mTORC1/2 inhibiting agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with AZD2014, breastfeeding should be discontinued if the mother is treated with AZD2014.

3.2.23 HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with AZD2014. In addition, these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

3.2.24 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca, CRO staff, and/or staff at the CPU)

Note: Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be initiated on study treatment. There can be no exceptions to this rule, although during protocol development, discussions about certain criteria are possible and may be amended, depending on new data and specific study requirements. Where patients that do not meet the inclusion criteria are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the Investigator should inform the AZD2014 team immediately. The AZD2014 team is to ensure all such contacts are appropriately documented.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

AZD2014 will be administered orally at a dose of 125mg (two 50mg tablets and one 25mg tablet) twice daily for two consecutive days out of every seven days, with 28 consecutive days defined as a treatment cycle (1 cycle = 28 days). Treatment will be administered on an outpatient basis. Patient must take drug on the same two days of each week. This can be adjusted only in extenuating circumstances and with approval from the Site PI. In cases where the treatment days are modified, subjects should not advance more than 1 day earlier (e.g., Tuesday/Wednesday to Monday/Tuesday is acceptable but Tuesday/Wednesday to Sunday/Monday is not acceptable) or 2 days later (e.g., Tuesday/Wednesday to Thursday/Friday is acceptable but Tuesday/Wednesday to Friday/Saturday is not acceptable). Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's neoplasm.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose*****	***Route***	***Schedule***	***Cycle Length***
AZD2014	Can be taken with or without food	125 mg	Oral	Twice per day on 2 consecutive days of every 7 days	28 days (4 weeks)

Patients will record dosage information and timing in the drug diary in appendix E. Additionally, patients will bring AZD2014 bottles and any remaining pills to each clinic visit for manual reconciliation of pill numbers.

Food restrictions
AZD2014 can be taken with or without food.

- The first dose of the day should be taken at approximately the same time each morning
- The second dose of the day should be taken approximately 12 h after the morning dose
- Large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g. grapefruit juice or marmalade) should be avoided whilst taking AZD2014
- No more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily is allowed

If vomiting occurs within 30 minutes after AZD2014 dosing, or later if the tablet(s) can be identified in the vomit content, the patient can re-take new tablet(s).

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD2014 tablet(s) on time.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Day 1 of Cycle 1, the following eligibility criteria from baseline evaluation must be met:

- Negative pregnancy test
- ECOG performance status ≤ 2 (Karnofsky $\geq 60\%$)
- Mean resting QTcF (QT with Fredericia correction) <470 msec as per local reading
- leukocytes $\geq 3{,}000$/mcL
- absolute neutrophil count $\geq 1{,}500$/mcL
- hemoglobin ≥ 9.0 g/dL
- platelets $\geq 100{,}000$/mcL
- total bilirubin ≤ 1.5 x institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) $\leq 2.5 \times$ institutional upper limit of normal
- Serum creatinine ≤ 1.5 x institutional upper limit of normal concurrent with creatinine clearance ≥ 50 mL/min (measured or calculated by Cockcroft and Gault equation)

If patients do not meet the criteria listed above on the day of treatment, treatment may be delayed for up

to two weeks (not to exceed 28 days from screening). Repeat labs should be repeated in 7 days.

5.2.2 Subsequent Cycles

During a cycle of treatment, AZD2014 should continue to be administered as planned unless toxicity has occurred which required treatment hold, as defined in Section 6 and table 3. In order for retreatment to begin, all hematologic and non-hematologic toxicity considered to be related to AZD2014 must have resolved to CTCAE grade 1 or baseline within 14 days. If the patient fails to meet the above-cited criteria for retreatment, then initiation of the next cycle of treatment should be delayed. Should treatment need to be delayed for more than 19 days because of inadequate recovery from toxicity related to AZD2014, subject should be withdrawn from treatment.

5.3 Agent Administration

5.3.1 AZD2014

AZD2014 should be taken at a dose of 125mg (two 50mg tablets and one 25mg tablet) orally twice daily on two consecutive days out of every seven days (i.e., 2 days of drug followed by 5 days of rest). Patient must take drug on the same two days of each week. This can be adjusted only in extenuating circumstances and with approval from the Site PI. The length of one cycle is 28 days (1 cycle = 28 days). Tablets should not be crushed.

Where possible all doses of AZD2014 should be taken at approximately the same times each day. Twice daily doses should be taken approximately 12 hours apart. If vomiting occurs within 30 minutes after AZD2014 dosing, or later if the tablet(s) can be identified in the vomit content, the patient can re-take a new tablet(s).

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD2014 tablet(s) on time.

Sunlight-protection measures
Patients should be advised of the need for sunlight protection measures such as use of sunscreen during administration of AZD2014, and should be advised to adopt such measures for a period of three months after receiving their final dose of AZD2014.

Caregivers should take precaution in handling AZD2014, should wear gloves when in contact with the tablets or when cleaning up vomitus contining the tablets. Pregnant women should avoid contact with the tablets altogether.

5.4 General Concomitant Medication and Supportive Care Guidelines

While patients may not enter a study arm if they have taken within the stated washout periods prior to study start any of the CYP3A4/5, Pgp (MDR1) or BCRP inhibitors or inducers detailed in Appendix B, it

could be possible to allow their short-term administration during the study under the following circumstances:

- If a patient requires short-term administration of a drug that is a potent or moderate CYP3A4/5, Pgp or BCRP inhibitor this could be permitted, but may increase exposure to study drug which must be withheld for three days prior to the first dose and not restarted until at least the concomitant therapy has been discontinued and the subsequent washout period described in Appendix B has been reached.
- If a patient requires short-term administration of a drug, which is a potent or moderate CYP3A4/5, Pgp (MDR1) or BCRP isoenzyme inducer this should be clearly documented in the Case Report Form (CRF) and may then be permitted, but the Investigator will be informed that this could lead to lower levels of study drug and a potential reduction in clinical efficacy.

All patients should avoid concomitant use of sensitive or narrow therapeutic range **substrates** of OATP1B1, OATP1B3, OCT1 and OCT2 detailed in Exclusion criteria and appendix B from the time they enter the screening period until 2 weeks after the last dose of treatment, ensuring no study treatment is started until the wash-out period appropriate for each drug has elapsed (at least 5 x elimination half-life). However it could be possible to allow their short-term administration during the study under the following circumstances:

- If a patient requires short term administration of substrates of BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 enzymes / transporters it may be permitted but for **sensitive or narrow therapeutic range substrates** (see tables in Exclusion criteria) the study drug should be withheld for 3 days prior to the first dose and not restarted until the concomitant therapy has been discontinued and the appropriate washout period (at least 5 x elimination half-life) has elapsed.

The lists of CYP inhibitors, inducers and substrates are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD2014 is safe.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, patients taking regular medication, with the exception of potent or moderate inhibitors or inducers of CYP3A4/5 Pgp (MDR1) or BCRP, should be maintained on it throughout the study period.

Patients who begin Coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving AZD2014 and should stop medication with AZD2014 at thrombocytopenia CTCAE Grade 3 or higher.

Patients may continue to receive therapeutic bisphosphonates and erythropoietin preparations (Procrit, Epogen, Aranesp), if they were receiving them prior to beginning study treatment.
Blood transfusions are allowed during the study.

Other medication that is considered necessary for the patient's safety and well-being may be given at the discretion of the investigators.

Because there is a potential for interaction of AZD2014 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the

participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix B presents a list of agents known to induce or inhibit these isoenzymes that could potentially interact with the study agent(s).

Subjects should be advised of the need for sunlight protection measures during administration of AZD2014, and should be advised to adopt such measures for a period of 3 months after receiving their final dose of AZD2014.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Radiographic progression of NF2-associated tumors (e.g., target VS, contralateral VS, or ependymomas) that require additional or alternate therapies (NOTE: Growth of NF2-associated tumors that is consistent with the natural history of the disease is not a criterion for discontinuing protocol therapy.)
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy. In this scenario, the subject does not wish to take protocol-specified product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in any or all subsequent study visits or procedures). Subjects may decline to continue receiving protocol-specified product at any time during the study. If this occurs, the investigator will discuss with the subject appropriate procedures for withdrawal from protocol-specified therapy. These subjects, as well as those who have stopped receiving protocol-specified product(s) for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations at the discretion of the principal investigator.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Scott Plotkin, MD, PhD at [redacted].

5.6 Duration of Follow Up

Participants will be followed for 30 days from the last dose of study medication or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Subject completed required 30 day follow up
- Lost to follow-up
- Withdrawal of consent for data submission. In this scenario, the subject does not wish to take protocol-specified product any longer and is not willing to collaborate in providing further data by continuing on study (e.g., participate in any subsequent study visits or procedures).
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following subsections and tables. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

A dose of AZD2014 in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to AZD2014, and the treatment of overdose should be supportive for the underlying symptoms. To date, no subject has experienced an overdose with AZD2014 which was associated with adverse events. Overdoses with non-AZ2014 products used in combination or comparative studies should be managed according to the product label.

AZD2014 is expected to be well tolerated. Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Subjects who

require drug hold for > 19 days should discontinue study drug. In addition, subjects who require a dose hold should restart AZD2014 on the same two consecutive days of the week. For example, subjects who take drug on Mondays and Tuesdays should restart AZD2014 on Mondays and Tuesdays. For each patient, a maximum of 2 dose reductions will be allowed. The reduced dose level is presented in Table 2.

TABLE 2 AZD2014 DOSE LEVEL MODIFICATION

Dose level	AZD2014 Intermittent Dose
Starting Dose	**125 mg BID**
-1 Dose Level	100 mg BID
-2 Dose Level	75 mg BID

6.1 Dose modification and discontinuation criteria

Dose reduction and discontinuation guidelines for hematologic and non-hematologic toxicities are shown in Table 3. Dose re-escalation is not permitted. Subjects who require drug hold for > 19 days should discontinue study drug. In addition, subjects who require a dose hold should restart AZD2014 on the same two consecutive days of the week.

If a patient experiences a clinically significant and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, dosing will be interrupted or the dose reduced and supportive therapy administered as required.

If the toxicity resolves or reverts to ≤ CTCAE grade 2 within 2 treatment weeks and the patient is showing clinical benefit, treatment with AZD2014 may be restarted. If the toxicity does not resolve to ≤ CTCAE grade 2 after 2 weeks of treatment then the patient should be withdrawn from the study and observed until resolution of the toxicity. Maximal drug holiday allowed is 2 weeks. For an intermittent dosing cohort the maximum number of days allowed is 19 days (14 days + 5 from the drug holiday in Week 1, which still counts as "treatment week"). Subjects who require drug hold for > 19 days should discontinue study drug.

TABLE 3 DOSE MODIFICATIONS AND DISCONTINUATION CRITERIA FOR HEMATOLOGIC AND NON-HEMATOLOGIC TOXICITIES

NCI CTCAE Toxicity Grade	Action
Grade 0, 1, or 2	None
Grade 3 or 4 and/or clinically significant[a, b] Expected and likely manageable/reversible with dose reduction	Hold study drug

Toxicity remains (despite dose reduction) Grade 3-4 or is clinically significant[a] for ≥ 19 days	Discontinue study drug
Toxicity lasts ≤ 14 days and resolves to ≤ Grade 2 or is no longer clinically significant	Reduce dose level per Table 2 and restart
Toxicity is hematological Grade 4 (excluding anemia) lasting ≥ 4 days	Discontinue study drug
Grade 3 or 4 and/or clinically significant Not expected to be manageable/reversible with dose reduction	Discontinue study drug
Recurrence of Grade 3 events[a,b]	Reduce one more dose level if available (see Table 1), or if not discontinue study drug
Recurrence of Grade 3 cardiac event[a]	Discontinue study drug
Recurrence of Grade 4	Discontinue study drug

[a] Includes cardiac events such significant change in CK/CK-mb ratio (relative index >5%), increases in heart rate of +25 bpm (up to 100-125 bpm for more than 24hrs or increase in heart rate >125 bpm for more than 12 hours), recurrent or persistent (>24 hours) or symptomatic increases in blood pressure (increases by >20 mmHg diastolic or >156/100 mmHg) despite standard antihypertensive treatment, QTcF prolongation >500 ms.

[b] Note: for grade 3 or 4 asymptomatic hypophosphatemia, dose reduction is not required if toxicity lasts ≤ 14 days and resolves to ≤ Grade 1. Oral supplementation for repletion is allowed.

6.2 Management for specific adverse events

6.2.1 Recommendation for Treatment of Nausea, Vomiting, and Diarrhea:

In order to decrease the incidence of nausea and vomiting, an anti-emetic regimen is suggested for patients who develop nausea after starting AZD2014 for the first time. On subsequent dosing days, the following antiemetics should be administered and continued throughout the AZD2014 dosing days (e.g., 2 days on, 5 days off). If necessary, antiemetics can be administered continuously.

Serotonin (5-HT3) antagonist (choose one from this list below):

- Dolasetron 100 mg by mouth daily
- Granisetron 2 mg by mouth daily or 1 mg by mouth twice a day
- Ondansetron 16-24 mg by mouth daily

If nausea and vomiting are not being managed with the regimen above, start a breakthrough treatment with the addition of one agent of a different drug class, e.g.:

- Dexamethasone 8 mg PO at day 1 of the AZD2014 dosing period or
- Metoclopramide 10-40 mg PO or
- Olanzapine 5-10 mg PO or
- Promethazine (Phenergan)12.5 – 25 mg every 6 hours

on the AZD2014 dosing days prior to the AZD2014 dose.

If this is still not managing the nausea/vomiting sufficiently, add Lorazepam 0.5-2 mg by mouth or sublingual every 4 to 6 hours as needed, but only on the AZD2014 dosing days. If necessary, dosing on all days can be permitted after discussion with the study PI.

If stomach pain develops, a H2 blocker or proton pump inhibitor can be added but should be taken only on days when AZD2014 is not given (during drug holidays).

An unscheduled serum urea and creatinine test should be performed in every case of an SAE > grade 1 of diarrhea.

6.2.2 Recommendations for Treatment of Diarrhea

Patients should be made aware of the risk of diarrhea while receiving treatment with AZD2014. Patients should be advised to drink sufficient fluids and have a supply of loperamide available throughout treatment. However, loperamide should not be administered prophylactically.

As soon as the first liquid stool occurs, patients should start treatment with loperamide immediately and also take electrolyte-containing fluids. Patients should inform their study doctor.

The recommended antidiarrheal treatment is loperamide, to be administered as per package information and usual clinical practice. Loperamide should not be administered for more than 48 consecutive hours.

If the diarrhea is unresponsive, dose reduction or interruption should be considered.

6.2.3 Recommendations for Treatment of Stomatitis/Oral Mucositis/Mouth Ulcers

For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times immediately after drug administration (1 to 3 hours) and during the day as required until resolution.

For more severe toxicity (Grade 2 or 3), the suggested treatments are topical analgesic mouth treatments (i.e., local anaesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenolic compounds), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (e.g., Kenalog in Orabase®) or alcohol-free 0.5 to 2 mg/5 mL dexamethasone oral solution (i.e., for example Dexsol® or PMS Dexamethasone 0.5 mg/5 mL Elixir). The mouth rinse will be self-administered at a daily dose of 10 mL 3 times per day. **Most importantly**, patients must be instructed to swish and expectorate the mouth rinse to avoid systemic exposure to dexamethasone. Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid

these agents.

For Grade 3 stomatitis/oral mucositis/mouth ulcers, systemic pain killers are indicated (e.g. oral or s.c. morphine) and dose modification as described in Section 6.

AZD2014 should be stopped until stomatitis improves to ≤ Grade 1, and then resumed without a dose reduction. If the toxicity does not resolve to ≤ CTCAE Grade 2 after two treatment weeks, then the patient should either be withdrawn from study treatment or discussed individually with the medical monitor if the patient derives clinical benefit. If Grade 2 to 3 stomatitis recurs, dose reduce AZD2014.

6.2.4 Recommendations for Treatment of Decreased Appetite

Decreased appetite should be treated according to local clinical practice. Dietary review is recommended.

6.2.5 Recommendations for Treatment of Rash/Skin toxicity

Early identification and intervention is critical for the optimal management of rash. Preliminary clinical evidence suggests that antihistaminergic drugs may ameliorate occurance/severity of rash. Therefore, patients who develop Grade 1 or 2 changes in their skin condition should be treated with the Investigator's choice of antihistaminergic drugs, over the counter moisturizing cream or ointment, local antihistamines and/or topical or systemic steroids. If bacterial infection is suspected, local and/or systemic antibiotics may be added.

For Grade 3 rash, topical and/or systemic steroids with or without topical and/or systemic antibiotics (to be considered if bacterial infection is suspected) are indicated, together with dose modifications as described in Section 6; short courses (≤14 days) of corticosteroid treatment at doses that do not exceed 100 mg per day of prednisone or equivalent may be given.

Some example treatments are listed below.

- Topical steroids: triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone proprionate 0.05%, aclometasone 0.05%
- Topical antipruritics: pramoxine 1%; doxepin 5% cream
- Oral antihistamines: loratidine, cetirizine, fexofenadine; diphenhydramine 25-50 mg every 8h; hydroxyzine 25 mg every 8h
- Topical antibiotics: clindamycin 1-2%; erythromycin 1-2%; metronidazole 1%; silver sulphadiazine1%
- Oral antibiotics: doxycycline 100 mg BD; minocycline 100 mg BD; oxytetracycline 500 mg

6.2.6 Recommendations for Treatment of Hyperglycemia

In general management of hyperglycemia should be performed according to local standards at the discretion of the investigator. Due to the predicted short half-life of AZD2014, only a short period of hyperglycemia with insulin resistance might be expected. Therefore early treatment with insulin and/or oral anti-diabetes medication should be carefully evaluated and blood sugars and hypokalemia monitored as per standard clinical practice. If blood glucose levels are < 250 mg/dl (Grade 2), generally no medical treatment is required. Dietary modification may be initiated.

For ≥ Grade 3 hypergycemia, dose modifications are required (see Section 6).

6.2.7 Recommendations for Evaluation and Treatment of Interstitial Lung Disease

A baseline thorax CT scan must be available for all patients treated with AZD2014, for retrospective analysis and comparison with a high resolution CT scan, should it be required, when symptoms occur during trial conduct. Should a patient experience any new respiratory symptoms including cough, dyspnea, lower respiratory tract infections not clearly explained by other factors such as disease progression or anemia, a high resolution CT scan and pulmonary function tests should be performed, including 3 forced expiratory volumes, forced vital capacity, and carbon monoxide diffusing capacity (DLCO% & DLCO).A recent hemoglobin measurement should also be available at the time of the DLCO evaluation. If these investigations are suggestive of pneumonitis or interstitial lung disease and causality with the study drug cannot be excluded, treatment should be interrupted. In more severe cases treatment with corticosteroids should be considered.

6.2.8 Recommendations for Evaluation and Management of ECG Changes

T wave changes on the ECG have been observed in 9 selected patients of the total 135 included in the study 1**:** 4 patients had AE of T wave inversion reported by Investigator. Additional 5 patients' ECG were assessed as potentially significant as the T wave changes were persistent on treatment and did not resolve at end of study. However, the above mentioned ECG findings do not indicate a clinically significant ECG abnormality when the pre-clinical CV safety profile of the study compound and the clinical context of the observed ECG changes are taken into the final clinical consideration.

Patients who develop persistent, confirmed T wave repolarisation abnormalities (inversion or flattening) on regularly scheduled ECGs may be referred for a cardiology opinion. The following studies should be performed:

- ECG monitoring:
  - Screening
  - beginning of cycle 2
  - every other cycle
  - trial discontinuation
  - 30 day follow-up visit
- Troponin t measurement
  - Should be performed within 24-hours if a new T-wave abnormality (such as T wave inversion or flattening or other repolarisation is recorded (and as clinically indicated)
  - trial discontinuation

- LV function assessment:
  - Screening
  - During treatment as clinically indicated
  - trial discontinuation
  - 30 day follow up visit in any case an abnormal LV function was diagnosed (to document recovery while off drug)

6.2.9 Recommendations for Evaluation and Treatment of Liver function tests abnormalities

Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of serum glutamic oxaloacetic transaminase (AST), Alanine transaminase (ALT) or serum bilirubin should trigger an investigation of the cause which may include viral infection. If hepatic dysfunction is thought to be a consequence of treatment with AZD2014, treatment interruption and/or reduction should be considered. The investigator should consider whether the abnormal liver function meets the criteria for expedited reporting.

6.2.10 Recommendations for Evaluation and Treatment of Severe Fatigue

If ≥ Grade 3 fatigue occurs, the dosing should be held for up to 14 days (up to 2 full treatment weeks) before being restarted at a lower dose.

Routine clinical work-up to exclude reasons other than the underlying disease and/or AZD2014 treatment may be performed, including laboratory analyses to rule out metabolic (acidosis, hyperglycemia) or cardiac problems.

7. ADVERSE EVENTS AND REPORTING REQUIREMENTS

7.1 Adverse Event Characteristics

7.1.1 Definitions of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.1.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

7.2 Recording of adverse events

7.2.1 Time period for collection of adverse events

Adverse Events will be collected from time of first dose of study drug throughout the treatment period and including the 30-day follow-up period. SAEs will be recorded from the time of informed consent until the 30-day follow-up period.

7.2.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

7.2.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- max CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be

utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event as noted below. For SAEs, causal relationship will also be assessed for other medication and study procedures.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.2.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs etc should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

7.2.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN should be reported as SAEs (see appendix C).

7.2.8 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing meningiomas under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

7.2.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer. Symptoms of metastases or the metastases itself should not be reported as an AE/SAE as they are considered to be disease progression.

7.2.10 Overdose

There is currently no known antidote to AZD2014. The treatment of AEs associated with overdose should be supportive for the underlying symptoms. Doses of study treatment in excess of that specified in the clinical study protocol are considered to be an overdose. Should an overdose (accidental or deliberate) occur, all symptoms associated with the overdose should be reported as AEs.

7.2.11 Pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study. All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

AZD2014 should not be administered to pregnant or breast-feeding women. It is recommended that non-childbearing status should be confirmed by a negative pregnancy test before administration of AZD2014 in women of childbearing potential.

Conception must be avoided during maternal or paternal exposure to AZD2014.

Females of child-bearing potential must use two forms of highly effective contraception (per institution standards) from the time of screening until 4 weeks after discontinuing study treatment. Acceptable methods of contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

or must fulfill the following criteria:

- Male partners sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- True abstinence

Male patients should use condoms and refrain from donating sperm from the start of dosing until 16 weeks after discontinuing study treatment. If not done previously, storage of sperm prior to receiving AZD2014 will be advised to male patients with a desire to have children.

Male patients should abstain from sperm donation during exposure to AZD2014.

It is not currently known whether AZD2014 affects fertility in humans.

AstraZeneca should be notified of any pregnancy that occurs in female patients or partners of male patients during participation in studies of AZD2014.

7.3 Adverse Event Reporting

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. All SAEs have **to** be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, the Sponsor must ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site (DES) within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

All follow-up information or corrections to data previously submitted on SAEs must be sent to the AstraZeneca DES within the same timelines specified above for the initial reporting. If the follow-up makes the case fatal or life-threatening (or if it is related to an existing fatal/life-threatening case) it must be sent to the AZ Patient Safety Data Entry Site within 1 calendar day.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Sponsor must inform the AstraZeneca DES immediately, or no later than 24 hours of awareness of it. For overdoses associated with a SAE, the standard reporting timelines above apply. For other overdoses, reporting must occur within 30 days.

If any pregnancy occurs in the course of the study, then the Sponsor must inform the AstraZeneca DES within 1day i.e., immediately but no later than 24 hours of awareness of it.

7.3.1.1 Contact information for reporting of SAEs to AZ Patient Safety Data Entry Site (DES)

Tata Consultancy Services (TCS) will be responsible for processing all SAEs onto the AZ Patient Safety Database. The following Clinical trial mailbox should be used:
AE Mailbox Clinical Trial (TCS) - [redacted]

If the system is unavailable, the Sponsor should fax the SAE report to the TCS immediately, recognizing that the same reporting time frames still apply.

Fax number: [redacted]

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

AstraZeneca shall be responsible for reporting AEs that are received during the study to regulatory bodies outside of the USA.

The Sponsor will be prompted on a regular basis, by the designated AstraZeneca Representative, to provide a listing of all AEs/expedited AE reports submitted to the local regulatory authority. This list is reconciled against the record of AEs/expedited AE reports received by AstraZeneca.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Expected Toxicities

Section 5.4 (Emerging Safety profile) of the AZD2014 Investigator's Brochure lists those AEs and laboratory abnormalities that are currently regarded as expected for regulatory reporting purposes, i.e. decreased appetite, lethargy, diarrhea, nausea, vomiting, stomatitis, fatigue/asthenia, mucositis, rash (including rash maculopapular, rash macular, rash papular, rash erythematous, dermatitis acneiform), decreased appetite, hypokalemia, hypophosphatemia, hyperglycemia.

A full description of the emerging safety profile for AZD2014, with guidance for investigators, is provided in Section 6 of the IB.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

The Sponsor will provide AstraZeneca the non-serious AEs as a listing every 3 months until the end of the study.

7.8 Periodic reporting requirements and ISLs

The Sponsor shall forward to AstraZeneca any periodic study reports that are required by the local regulatory authority (e.g. IND annual reports; annual and 6-monthly safety reports), as well as any IRB/IEC updates.

AstraZeneca shall provide the Sponsor with copies of all ISLs relating to the study drug and issued by or available to AstraZeneca. The Sponsor shall be responsible for providing copies of these ISLs to the Institution, IRB/Ethics Committee, and to any other participating investigators at the Institution as applicable to local regulations.

7.9 Significant new safety issues

The Sponsor shall notify AstraZeneca of any 'significant' (defined as an issue that requires alteration of the informed consent form for the study or constitutes a significant change to the benefit:risk of the study) new safety issues as soon as possible, and at least in parallel with any correspondence to regulatory authorities.

7.10 Independent Medical Monitor

The Research Monitor, Aerang Kim, MD, PhD, is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will

review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress; remove individual human subjects from a research protocol; take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

7.11 End of Study

The Sponsor shall inform AstraZeneca when the study has completed and provide AstraZeneca with a listing of all AEs, both serious and non-serious. The Sponsor should also provide AstraZeneca with a copy of the final Clinical Study Report.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 AZD2014

8.1.1 Description

The chemical name is: 3-[2,4-Bis((3S)-3-methylmorpholin-4-yl)pyrido[5,6-e]pyrimidin-7-yl]-N-methylbenzamide. The molecular formula is $C_{25}H_{30}N_6O_3$.

Other Names. None

Classification. Selective inhibitor of mTOR kinase

Molecular Weight. Approximate molecular weight is 426.54

Mode of Action. Mammalian target of rapamycin (mTOR) serine/threonine kinase (dual mTOR complex 1 and 2 inhibitor, mTORC1 and mTORC2)

Route of Administration. Oral

Terminal half-life. 5.1 to 9.4 hours

For further details and molecule characterization, see the AZD2014 Investigator Brochure.

8.1.2 Form

AZD2014 is presented as a plain, round, biconvex, yellow, film-coated tablets comprising two strengths, containing 25 or 50 mg AZD2014. The drug product is supplied in white, high-density polyethylene bottles with standard, lined, screw-neck closures. These bottles are child-resistant

and tamper-evident.

AZD2014 tablets contain AZD2014, mannitol, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate. The tablet film coat comprises polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc and yellow iron oxide.

8.1.3 Storage and Stability

AZD2014 tablets should be stored in the clinical pack at room temperature (below 30°C). For further information, investigators should refer to the investigational product label.

8.1.4 Handling

No specific recommendations for participants. Caregivers should take precaution in handling AZD2014, should wear gloves when in contact with the tablets or when cleaning up vomitus containing the tablets. Pregnant women should avoid contact with the tablets altogether.

8.1.5 Availability

AZD2014 will be supplied free of charge by AstraZeneca as bulk tablets. Bottling, packaging and labeling will be the responsibility of the investigator, and will be distributed to investigators through the research pharmacies in the respective participating institutions.

8.1.6 Preparation

AZD2014 will be provided in tablet formulation ready for ingestion as prescribed.

8.1.7 Administration

AZD2014 will be taken orally in tablet formulation

8.1.8 Ordering

AZD2014 will be provided by AstraZeneca and will be stored in the research pharmacy. AZD2014 will be available for dispensing from the institution prior to study activation.

8.1.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.10 Destruction and Return

At the end of the study, unused supplies of AZD2014 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies will be mandatory for all enrolled patients, and will be performed on archived meningioma tumor tissue from prior surgery(ies). We will perform targeted resequencing of *NF2* gene for all available archival formalin-fixed/paraffin-embedded (FFPE) or frozen meningiomas from patients enrolled in this study. Further, we will perform immunohistochemistry analysis of the same archived tumor samples for evidence of mTORC1 and mTORC2 pathway activation which have also been shown to be active in these tumor.[24,30,35]

9.1 Biomarker Studies

9.1.1 Rationale

Chromosome 22q loss and *NF2* mutations are known to occur in all meningiomas and schwannomas associated with NF2. We propose to perform targeted resequencing of *NF2* in all available primary and recurrent tumors for patients enrolled in this study. This genetic information will not only allow us to draw the conclusion whether there is a correlation between response to AZD2014 and genetic variation in *NF2*, but could also serve as valuable biomarker(s) for drug efficacy. Further, meningiomas and schwannomas with *NF2* loss reveal strong activation of mTORC1 and mTORC2 signaling. Therefore, as an additional correlation, we propose to perform immunohistochemistry (IHC) analyses of mTORC1, mTORC2 signaling for all available archival meningioma and schwannoma samples of patients enrolled in this study.

9.1.2 Genetic Analyses of meningiomas and schwannomas

The *NF2* gene on chromosome 22q12.2 spans 95,045 bp encoding 17 exons. For targeted resequencing, we will take the approach of PCR amplification of each coding exon, along with ~50 bp of flanking (5' and 3') intronic sequences, followed by Sanger sequencing. We have extensive experience in this approach including sequencing of *NF2*, *TSC1,* and *TSC2* genes for mutational analyses of respective NF2 and TSC patients when these genes were originally identified [36-39]. Fresh meningioma and schwannoma samples are routinely collected at MGH after surgery for culturing meningioma cells as well as for banking as frozen tumor samples. Due to the presence of multiple meningiomas and schwannomas in NF2 patients, many of which are managed surgically, we may have more than one tumor specimen available from some of the enrolled patients. Thus, we anticipate assembling a cohort of 25-30 tumors, either as frozen or as formalin-fixed/paraffin-embedded samples for resequencing. DNA extracted from these tumors will be PCR amplified and sequenced on an ABI3730 capillary sequencer, and sequence analysis will be performed using Sequence Scanner software version 1.0 (Applied Biosystems). We predict *NF2* mutations in the majority of meningiomas and schwannomas. Genetic variations in *NF2* will be correlated with the drug response. No germline mutation analysis of the *NF2* gene will be performed.

9.1.2 Immunohistochemical analyses of meningiomas and schwannomas

For IHC analyses, we have chosen phospho-S6 (pS6, Ser240/244) and phospho-4E-BP1 (p4E-BP1, Thr37/46) as the mTORC1 pathway readouts and SGK1 target phospho-NDRG1 (pNDRG1, Thr346) and phospho-Akt (pAkt, Ser473) as mTORC2 pathway readouts. IHC staining for these proteins are well established with the commercially available antibodies. Formalin-fixed/paraffin-embedded or frozen archival meningioma specimens and where possible, schwannoma samples for patients enrolled in this

study will be obtained from the two participating sites (MGH, DFCI), and we anticipate obtaining at least 25-30 tumors for staining. Tissue diagnosis should be available for all archival tumors. Only NF2-related neoplasms will be evaluated. IHC staining will be performed as previously described [31] and will be examined by Dr. Stemmer-Rachamimov, an expert neuropathologist for NF tumors. Staining will be scored as weak (+), medium (++), strong (+++) or negative (0). Based on our extensive studies on NF2-associated tumors, we predict a majority of the tumors to show strong staining for mTORC1 and mTORC2 signaling.

The correlative studies will be useful in determining whether a specific type of *NF2* mutation(s) in the tumors and/or the level of mTORC1 and mTORC2 activation is associated with response to AZD2014 treatment.

We also plan to collect two samples of blood from each patient, one just before the initiation of this trial and a second sample at the end of the trial for isolation and storage of plasma and buffy coat. These samples will be frozen for transcriptome and other relevant biomarker studies that could be undertaken in the future (with IRB approval).

9.2 Laboratory Correlative Studies

9.2.1 Genetic and immunohistochemical analysis of archived tumor tissue

9.2.1.1 Collection of Specimen(s)
Prior to screening, patients may have an archival formalin-fixed/paraffin embedded tumor or frozen tissue block (or 5 unstained slides) from a previous surgery available. The tumor blocks or slides will be delivered to the care of Dr. Vijaya Ramesh, Center for Human Genetic Research, Massachusetts General Hospital, with a prepared label (see below).

9.2.1.2 Handling of Specimens(s)
All tumor blocks and slides should be shipped with labels according to the template below. Study sites will be responsible for costs of shipping and shipping materials. Labels should include study number (protocol number), subject ID (participant study number), site investigator, institution, case number (per local pathology records), number of blocks (if applicable), and date of mailing. All samples must be de-identified. Frozen tissue samples should be mailed on dry ice.

A label example is provided below:

Study No.:	Subject ID.:
Site investigator:	Study site:
Case No.:	No. of blocks:
Date of mailing:	
Type of specimen (*unstained slides, frozen tissue block, paraffin-embedded tissue block*):	

9.2.1.3 Shipping of Specimen(s)
All appropriately labeled and de-identified tumor samples should be sent in 1 batch, or as requested by the Coordinating Center after patient registration, and overnight shipped to:

Dr. Vijaya Ramesh Laboratory
Attn: Roberta Beauchamp
[redacted]

** Please email Dr. Vijaya Ramesh ([redacted]), Roberta Beauchamp ([redacted]), and the Coordinating Center ([redacted]) to notify of shipment prior to sending. Shipments can only be scheduled for weekday arrival between 9 am and 4 pm (1 pm on Fridays).

9.2.1.4 Site(s) Performing Correlative Study

Correlative studies will be performed by the laboratory of Dr. Vijaya Ramesh, Center for Human Genetic Research, Massachusetts General Hospital, in collaboration with Dr. Stemmer-Rachamimov, Department of Pathology, Massachusetts General Hospital. FFPE specimens will be processed for total nucleic acid extraction by commercially available kits. DNA extracted from these tumors will be PCR amplified and sequenced on an ABI 3730 capillary sequencer, and sequence analysis will be performed using Sequence Scanner software version 1.0 (Applied Biosystems). IHC staining will be performed as previously described [31] and will be examined by Dr. Stemmer-Rachamimov. Staining will be scored as weak (+), medium (++), strong (+++) or negative (0).

9.2.2 Blood samples for future studies

9.2.2.1 Collection of Specimen(s)

At baseline and at the end of study, a sample of blood should be collected from subjects. Blood samples will be delivered to the care of Dr. Vijaya Ramesh, Center for Human Genetic Research, Massachusetts General Hospital, with a prepared label (see below

9.2.2.2 Handling of blood specimens(s)

Peripheral blood will be drawn, with informed consent, from antecubital vein into appropriate 10 cc ACD (acid-citrate-dextrose) anticoagulant containing tubes (e.g. ACD Vacutainer® supplied by Becton Dickinson) provided by the study site. Tubes should be gently shaken for the anti-coagulant to mix. The tube should be shipped to the Ramesh laboratory (see below) within 1 day of drawing the sample to the address below (section 9.2.2.3).

Blood samples should be shipped with labels according to the template below. Study sites will be responsible for costs of shipping and shipping materials. Labels should include study number (protocol number), subject ID (participant study number), site investigator, institution, case number (per local pathology records), and date of mailing. All samples must be de-identified.

A label example is provided below:

Study No.:	Subject ID.:
Site investigator:	Study site:

Date of mailing:	
Type of specimen: Blood sample for isolation of buffy coat and plasma	

In the laboratory, the blood sample will be layered aseptically on a cushion of thixotropic Ficoll-Hypaque® gel (e.g. BD vacutainer CPT tube) and centrifuged at 1800*g* for 30 minutes. The top plasma layer will be gently aspirated, barcoded, and stored at -80. The lymphocyte and monocyte containing layer (buffy coat) will be aspirated and placed in a 15mL conical tube, washed 2 times with 12mL of PBS (without Mg^{2+} and Ca^{2+}) by pelleting the cells at 470*g* for 15 minutes. The washed pellet will be re-suspended in 1mL FBS with 10% DMSO, bar-coded and cross referenced with plasma and stored frozen in liquid nitrogen vats

9.2.2.3 Shipping of Specimen(s)

All appropriately labeled and de-identified samples should be sent on ice within 1 day to Dr. Ramesh's laboratory. For samples drawn on Monday, Tuesday, Wednesday, or Thursday, the sample may be stored at room temperature. For samples drawn on Friday, please store in refrigerator until shipped. Please ship samples to:

Dr. Vijaya Ramesh Laboratory
Attn: Roberta Beauchamp
[redacted]

** Please email Dr. Vijaya Ramesh ([redacted]) Roberta Beauchamp [redacted], and the Coordinating Center [redacted] to notify of shipment prior to sending. Shipments can only be scheduled for weekday arrival between 9 am and 4 pm (1 pm on Fridays).

9.2.2.4 Site(s) Performing Correlative Study

Future studies will be performed by the laboratory of Dr. Vijaya Ramesh, Center for Human Genetic Research, Massachusetts General Hospital. These samples will be frozen for transcriptome and other relevant biomarker studies that could be undertaken in the future. Samples will be stored indefinitely in the Ramesh laboratory. All future studies will be approved by the institutional review board prior to analysis.

10. STUDY CALENDAR

Baseline evaluations are to be conducted $\leq$ 28 days prior to start of protocol therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

	Screening (within 28 days of start of study drug)	Day 1 of each cycle (+/-3 days)[r]	Odd Cycles Only (+/-3 days)	Even Cycles Only (+/-3 days)	Every 12 weeks (+/-3 days)	Every 24 weeks (+/-3 days)	End of Treatment (+/-3 days)[p]	30 Day Follow-up (+/-5 days) [o]
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Pregnancy Test	X							
Archival Tumor Tissue	X							
Medical History	X							
Physical Examination, Weight and Vital Signs[a]	X	X	X	X			X	X
Karnofsky Performance Status	X	X					X	X
Clinical Chemistry[b]	X	X					X[e]	
Hematology[d]	X	X					X[e]	
Lipid Panel and HbA1c [c]	X		X				X[e]	
Urinalysis[f]	X	X					X[e]	
Coagulation[g]	X	X					X[e]	
Cardiac Markers[h]	X	X					X[e]	
Concomitant Medications	X	X					X	
Dosing Compliance		X					X	
Adverse Events	X	X					X	X
High Resolution Chest CT[i]	X							
Echocardiology/MUGA[j]	X	X					X	
ECG[k]	X			X			X	X
MRI of Brain [q]	X				X		X	
Audiology [n]	X					X		
Research Blood Samples [l]	X						X	
Quality of Life Questionnaires [m]	X				X		X	

a A complete physical examination will be performed at the following time points: Screening Visit, Day 1 Every Cycle, End of Treatment Visit, 30-day Follow-up Visit. Vital signs (heart rate, systolic and diastolic blood pressure, respiration rate, weight, height (at screening only) and temperature)

b Clinical chemistry including Sodium, Potassium, Phosphate, Chloride, Creatinine, Urea Nitrogen, Calcium, Venous Bicarbonate HCO_3 Albumin, Total Protein, AST, ALT, Alkaline Phosphatase, Total Bilirubin, LDH , Serum Glucose/Insulin and C-Peptide, Serum Uric Acid.

c HbA1c, triglycerides, and cholesterol should be performed at baseline and on day 1 of every odd cycle.

d Hematology to include complete blood counts with differential.

e All patients with clinically significant abnormal laboratory results at treatment completion or study drug discontinuation visit are to be followed until the results return to normal (or patient's baseline), or until a valid reason, other than a drug-related effect, is identified

f Urinalysis will only be taken at screening and if clinically indicated. Additional assessments may be performed at the discretion of the investigator if clinically indicated.

g Coagulation testing to include PT, PTT, and INR. Measurement should be performed at baseline and thereafter if clinically indicated.

h Cardiac marker troponin t should be assessed at screening, at trial discontinuation, and as clinically needed.
Troponin t (additionally other cardiac markers, i.e. CK, CK-MB, AST and LDH depending on the investigators decision if clinically indicated) should also be assessed on identification of abnormal ECG findings, e.g. new repolarization abnormalities, found to be possibly clinically significant by investigator's judgment. A repeat cardiac marker assessment should also be performed 24 hours later if such changes have been observed (more detailed information see 6.2.8)

i The patient should undergo a chest CT scan prior to registration in order to document the lung parenchyma status at baseline. High resolution CT should be performed if clinically indicated by pulmonary symptoms any time during the study. For any new respiratory symptoms (cough, dyspnea, lower respiratory infection) not clearly explained by other factors (eg, dyspnea associated with substantial drop in hemoglobin), patients should have oxygen saturation measured. If <92%, the high resolution CT scan of the chest should be repeated and pulmonary function tests should be performed.

j An ECHO/MUGA should be performed at screening, at trial discontinuation, and when clinically indicated. In case of any treatment-emergent left ventricular dysfunction, the ECHO or MUGA should be repeated at the 30 days follow up visit to address the question of recovery, during the off-treatment period: see section 3.5 for more detailed explanation). Echocardiography should include assessment of left ventricular end-systolic volume, left ventricular end-diastolic volume and LVEF. If an Echocardiography scan cannot be taken, a MUGA scan to assess left ventricular ejection fraction (LVEF) will be conducted. The modality of the cardiac function assessments must be consistent within patient, i.e., if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patient should also be examined using the same machine and operator throughout the study wherever possible. Other alternative methods of assessments could be used additionally if they are a part of the local standard of care, or if the investigator considers them necessary for the therapeutic management of the patient. Important cardiac symptoms should be reported as AEs/SAEs and should be carefully evaluated in regard to developing of acute or worsening of chronic cardiac failure, especially in anthracycline treated patients. Congestive cardiac failure should be treated and followed according to standard medical practice.

k Three twelve-lead ECGs are required at screening. One ECG is required in remaining future visits.

ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study.

If an abnormal ECG finding at baseline is considered by the investigator to be clinically significant, it should be reported as a concurrent condition. During the study, clinically significant abnormal ECG findings not present at baseline should be reported as an AE. If present, the clinical signs and symptoms associated with the abnormal finding should be reported as the AE with the ECG abnormality given as explanatory information.
Troponin (additionally other cardiac markers, i.e. CK, CK-MB, AST and LDH depending on the investigators decision if clinically indicated) should also be assessed on identification of abnormal ECG findings, e.g. new repolarisation

abnormalities. A repeat cardiac marker assessment should also be performed 24 hours later, if such findings occur. The same Troponin isoform should be assessed at each of the visits.
An ECG should be performed at any cardiac event with symptoms that may be due to cardiac ischemia, or arrhythmia (such as chest pain or palpitations). An ECG will also be captured in all cases of dyspnea and pulmonary edema and additionally at the discretion of the investigator if clinically indicated.

l Two samples of blood will be collected, one just before the initiation of this trial and a second sample at the end of the trial for DNA isolation and storage of plasma and buffy coat.

m Quality of life questionnaires include Neurofibromatosis 2 Impact on Quality of Life (NFTI-QOL) and Penn Acoustic Neuroma-Quality of Life (PAN-QOL) questionnaires (Appendix F).

n Audiology will include measurement of pure tone thresholds and determination of word recognition scores as described in Appendix G. Participants who are deafened bilaterally or have no measurable word recognition score for > 3 months prior to screening do not require audiograms during the study. Audiograms should be performed < 28 days prior to prior to Day 1 (unless previously performed at Massachusetts Eye and Ear Infirmary as part of routine clinical care within 60 days of day 1), on day 1 (+/-5 days) every 24 weeks, and at end of treatment.

o Patients with an unresolved AE or SAE event at treatment completion or study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event.

p 30-day follow up can be performed in clinic or by phone. Outside laboratory studies are acceptable for this evaluation. Outside ECG is acceptable for subjects without abnormal ECG findings during the study.

q Disease evaluation by gadolinium-enhanced magnetic resonance imaging (Gd-MRI) of the brain will occur ≤21 days prior to first AZD2014 administration and then after every 3 treatment cycles (i.e., **every 12 ± 1 week**) up to End of Treatment visit.

r If approved by the site PI, a patient who has been on study drug for 6 months or longer may substitute a telephone visit in place of any visit that does not include MRI scans. Scheduled assessments at telephone visits will include EKG, clinical chemistry, hematology, urinalysis, and coagulation studies performed at an outside facility. Assessments that will be deferred include physical examination, weight, vitals, performance status, and dosing compliance.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 12 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the criteria proposed by Dombi and colleagues[40] for neurofibromatosis-associated lesions. Response and progression will not be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST)[41] or by MacDonald Criteria[42], since they may underestimate progression in these irregularly shaped tumors. However, linear measurements will be collected as part of the trial for comparison with volumetric measurements. All measurements will be performed on the axial MRI T1 post contrast images.

Target lesion: Investigators should identify a single target meningioma in all subjects.

Non-target lesions: Non-target meningiomas in this study include all meningiomas (excluding the

target meningioma) that have a volume of at least 1 ml at baseline. For the purposes of response evaluation, the volume of non-target lesions will be summed.

11.1.1 Disease parameters

Measurable Disease: Measurable lesions are defined as those that can be accurately measured using volumetric analysis of MRI scans. **NOTE:** Tumor lesions that are situated in a previously irradiated area are considered measurable.

Non-measurable disease: Non-measurable lesions include lesions that are obscured by artifact from auditory brainstem implants (ABIs) or lesions whose margins are completely obscured by neighboring tumors (*i.e.*, "collision" tumors) or are indistinct.

11.1.2 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation (cubic centimeters or ml). All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Conventional MRI. This guideline has defined measurability of lesions on MRI scans of 5mm slice thickness or less. All study MRI scans should include standard whole brain (5 mm slice thickness or less) imaging sequences as well as fine cuts through the internal auditory canal (3 mm slice, no gaps) to image vestibular schwannomas. In patients who have had surgery for tumors in the cerebellopontine angle, fat-saturation should be performed with the post-contrast sequences to compensate for the possible presence of post-operative fat packing. Study volumetric analysis should be performed on post-contrast sequences with the same slice thickness beginning at the baseline assessment.

11.1.3 Response Criteria

11.1.3.1 Evaluation of Target Lesions

Objective Status, To Be Recorded at Each Evaluation: Investigators should choose a target meningioma to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination as non-target lesions. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

Complete Response (CR): Complete disappearance of target lesion compared with baseline.

Partial Response (PR): Greater than or equal to 20% decrease in volume of the target lesion compared to baseline.

Stable/No Response: Does not qualify for CR, PR, or progression.

Progression: Increase of at least 20% increase in target meningioma compared to baseline, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

11.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Complete disappearance of all non-target meningiomas.

Partial Response (PR): Greater than or equal to 20% decrease in the total volume of all non-target meningiomas and no new lesions.

Stable/No Response: Does not qualify for CR, PR, or progression.

Progression: at least 20% increase in the total volume of all non-target meningiomas over baseline. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

11.1.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, a vascular structure). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.3.4 Evaluation of Best Overall Response

Best Overall Response: This will be calculated from the sequence of objective statuses. For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to Sections 11.1.3.1 and 11.1.3.2. If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e. g. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

11.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the baseline measurements, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the baseline measurements. Participants without events reported are censored at the last disease evaluation

11.1.5 Progression-Free Survival

Progression-free survival at 6 months (PFS6): Progression-free survival at 6 months (PFS6) is defined as the proportion of patients alive and without progression at 6 months.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.6 Response Review

Central review of radiographic responses will not be performed.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a single-arm, single-center, open label, phase II study to evaluate the efficacy, safety, and tolerability of AZD2014 in NF2 patients with progressive or symptomatic meningioma. The primary objective of the study is to estimate the radiographic response rate for the cohort.

Up to 30 patients will be enrolled (i.e., consented) in a single stage in order to treat a maximum of 18 patients with AZD2014. Subject replacement will be allowed for participants who never begin protocol therapy, are deemed ineligible, or are deemed not evaluable. Subjects will not be replaced for participant drop out.

AZD2014 will be administered at a dose of 125 mg (two 50mg tablets and one 25mg tablet) orally twice per day on 2 consecutive days out of every 7 days. One cycle will consist of 28 days (1 cycle = 28 days). Dose reductions or delays will be allowed, if toxicity is observed. AZD2014 will be administered until disease progression or unacceptable adverse events are observed, according to section 7. Otherwise, patients will remain on study medication under this protocol indefinitely.

Disease evaluation by gadolinium-enhanced magnetic resonance imaging (Gd-MRI) of the brain will occur ≤21 days prior to first AZD2014 administration and then after every 3 treatment cycles (i.e., every 12 ± 1 week) up to End of Treatment visit. Tumor assessment will be evaluated by the investigator by volumetric MRI analysis (see Section 11). No interim analysis is planned and thus, no stopping rules are in place.

13.2 Sample Size, Accrual Rate and Study Duration

A maximum of 18 evaluable subjects will be treated with AZD2014 in this trial. The estimated accrual rate is 1 subject per 1-2 months with an expected accrual period will be about 30 months. The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 12 months after the last patient is enrolled. Thus, the planned duration of this trial will be about 42 months.

TABLE 6 STUDY ACCRUAL TARGETS

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	1	+	1	=	2
Not Hispanic or Latino	10	+	6	=	16
Ethnic Category: Total of all subjects	11	+	7	=	18
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	1	+	0	=	1
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	10	+	7	=	17
Racial Category: Total of all subjects	11	+	7	=	18

13.3 Stratification Factors

No stratification will be performed for the primary analysis.

13.4 Interim Monitoring Plan

Interim monitoring will not be performed.

13.5 Analysis of Primary Endpoint

The primary objective of this aim is to test the efficacy of AZD2014 in this study population. In a study of 287 meningiomas in 74 NF2 patients with a mean follow up of 110 months[43], no meningiomas (0%) were noted to have tumor shrinkage. Sixty-six percent of tumors showed minimal to no growth (< 1 mm/year) while 33% showed radiographic evidence of growth > 1 mm/year. Treatment efficacy will be measured by the radiographic response rate. 18 patients will be treated and assessed for efficacy. This sample will have 90% power and 5% significance level (actual significance level achieved by this test is 1.4%) using one-sided binomial test to test the difference between a radiographic response rate of 20% vs. a historical control rate of 1%. If at least 2 patients achieve a radiographic response in the target meningioma, the null will be rejected in favor of the alternative and the treatment will be declared worthy of further investigation.

13.6 Analysis of Secondary Endpoints

The secondary endpoints include:

- Median PFS
- 6-month progression free survival (PFS6)

- Proportion of subjects with a radiographic response for non-target meningiomas
- Duration of radiographic response
- Frequency of adverse events (possibly, probably, or definitely) related to AZD2014 use in this patient population
- Radiographic response rate of vestibular schwannomas (defined as an decrease in VS volume by ≥ 20% compared to baseline)
- Proportion of patients with a hearing improvement and decline (response defined as a statistically significant improvement/decline in word recognition score compared with baseline score—Appendix G);
- QoL, as measured by the Neurofibromatosis 2 Impact on Quality of Life (NFTI-QOL) and Penn Acoustic Neuroma-Quality of Life (PAN-QOL) questionnaires
- Clinical outcomes stratified by genetic and immunohistochemical analysis
- Radiographic response rate of vestibular schwannomas

Progression-free survival: The progression-free duration will be measured from the time of registration to the date of tumor progression. Patients who have not progressed will be censored at the date they were last known to be alive. Kaplan-Meier methodology will be used to estimate progression-free survival, with the 95% confidence intervals based on Greenwood's formula.

Progression-free survival at 6 months (PFS6): PFS6 will be measured after 6 months of treatment. Kaplan-Meier methodology will be used to estimate progression-free survival, with the 95% confidence intervals based on Greenwood's formula.

Response rate for non-target meningiomas: The radiologic response rate will be reported for all patients in the study and for all patients who complete at least 12 weeks of treatment. The response rate will be determined for the total volume of non-target meningiomas compared to the baseline total volume. Radiologic response rates will be reported with exact 95% confidence limits.

Duration of radiographic response: The durability of radiographic response over time will estimated using the Kaplan-Meier method. The median of the duration of response time with 95% confidence limits will be reported. The proportion of patients free from tumor progression at weeks 6, 12, 18, and 24 (depending on duration of participation) will be reported with 95% confidence limits.

Audiometric outcomes: Secondary endpoints will include changes in word recognition scores, pure-tone averages (PTAs), and tinnitus questionnaire scores. These tests will be performed at baseline and every 24 weeks.

- Word recognition score: A hearing response will be defined as improvement in word recognition score above the 95% critical difference (Appendix G) for subjects with baseline word recognition score < 85% at baseline. Hearing decline will be defined as decline in word recognition score below the 95% critical difference (Appendix G) for subjects with baseline word recognition score > 8% at baseline. The hearing response rates will be reported for all patients eligible for hearing improvement/decline who complete at least 24 weeks of treatment. Hearing response rates will be reported with exact 95% confidence limits. The durability of hearing response over time will be estimated using the Kaplan-Meier method. The median time with 95% confidence limits will be reported.
- Pure tone average: A 12 dB change in 4-frequency Pure Tone Average will be considered

clinically significant. The proportion with this change will be estimated and an exact 95% confidence interval computed.

Frequency of adverse events: The safety analysis set will include all patients who received any amount of study treatment. Adverse events will be tabulated by using the MedDRA classification system. The severity of the adverse event will be graded using the CTCAE whenever possible. For adverse events that are not included in the CTCAE, the grading categories (mild, moderate, severe, life-threatening, and fatal) will be used. The frequency of subjects experiencing a specific adverse event will be tabulated by System Organ Class, grade, and relationship to study drug. In the by-subject analysis, a subject having the same event more than once will be counted only once.

Change in quality of life: The study will explore whether the treatment could improve the quality of the life of NF2 patients. Two instruments will be used in this study including the Neurofibromatosis 2 Impact on Quality of Life (NFTI-QOL) and Penn Acoustic Neuroma-Quality of Life (PAN-QOL) questionnaires. They will be implemented 4 times through the trial (baseline, 6 months, 12 months and off study (18 months). An overall score at each time point, as shown in Ferner et al.,[44] will be compared with the baseline score. Two-tailed pared t-test will be used to assess the change from the baseline

Clinical outcomes stratified by genetic and immunohistochemical analysis
Analysis of *NF2* in 25-30 tumors will allow for the estimation of efficacy parameters such as OS, PFS and RR. The relationship between genetic variation and these parameters will be assessed by the Log-Rank test. McNemar test will be utilized to demonstrate the concordance of the mTORC1 and mTORC2 pathways by IHC analyses of the tumors, and the Log-Rank test will also be used to test the differences between 0+1 and 2+3 groups in the mTOR signaling pathways and their relationship to treatment efficacy.

Response rate for vestibular schwannomas: The radiologic response rate will be reported for all vestibular schwannomas in participants who complete at least 12 weeks of treatment. We anticipate that 18-27 tumors will be available for analysis. The response rate will be determined for each vestibular schwannoma compared to the baseline volume. Radiologic response rates will be reported with exact 95% confidence limits

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

The safety analysis set will include all patients who received any amount of study treatment. All patients will be evaluable for toxicity from the time of their first treatment with AZD2014 until 30 days following their last dose of AZD2014.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All of the participants who met the eligibility criteria (with the exception of those who received no study medication) should be included in the main analysis of the response rate (intention-to-treat analysis). Participants with early death from toxicity, early death because of other cause, or with unknown status (not assessable, insufficient data) should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does

not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. **Evans DG, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* Jan 2005;26(1):93-97.**
2. **Mautner VF, Lindenau M, Baser ME, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. *Neurosurgery.* May 1996;38(5):880-885; discussion 885-886.**
3. **Smith MJ, Higgs JE, Bowers NL, et al. Cranial meningiomas in 411 neurofibromatosis type 2 (NF2) patients with proven gene mutations: clear positional effect of mutations, but absence of female severity effect on age at onset. *Journal of medical genetics.* Apr 2011;48(4):261-265.**
4. **Chamberlain M. Chemotherapy for Intracranial Meningiomas. In: DeMonte F MM, Al-Mefty O, ed. *Al-Mefty's Meningiomas, 2nd ed.* New York: Thieme; 2011.**
5. **Grunberg SM, Weiss MH. Lack of efficacy of megestrol acetate in the treatment of unresectable meningioma. *Journal of neuro-oncology.* Feb 1990;8(1):61-65.**
6. **Grunberg SMR, C; Townsend, C; et al. Phase III double-blind randomized placebo-controlled study of mifepristone (RU-486) for the treatment of unresectable meningioma [abstract]. 2001;20:221.**
7. **Goodwin JW, Crowley J, Eyre HJ, Stafford B, Jaeckle KA, Townsend JJ. A phase II evaluation of tamoxifen in unresectable or refractory meningiomas: a Southwest Oncology Group study. *Journal of neuro-oncology.* Jan 1993;15(1):75-77.**
8. **Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology.* Apr 13 2004;62(7):1210-1212.**
9. **Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with CPT-11 for recurrent meningioma. *Journal of neuro-oncology.* Jul 2006;78(3):271-276.**
10. **Newton HB, Scott SR, Volpi C. Hydroxyurea chemotherapy for meningiomas: enlarged cohort with extended follow-up. *British journal of neurosurgery.* Oct 2004;18(5):495-499.**
11. **Loven D, Hardoff R, Sever ZB, et al. Non-resectable slow-growing meningiomas treated by hydroxyurea. *Journal of neuro-oncology.* Mar-Apr 2004;67(1-2):221-226.**
12. **Rosenthal MA, Ashley DL, Cher L. Treatment of high risk or recurrent meningiomas with hydroxyurea. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia.* Mar 2002;9(2):156-158.**
13. **Wen PY, Yung WK, Lamborn KR, et al. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01-08). *Neuro-oncology.* Dec 2009;11(6):853-860.**
14. **Norden AD, Raizer JJ, Abrey LE, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *Journal of neuro-oncology.* Jan 2010;96(2):211-217.**
15. **Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro-oncology.* Jan 2015;17(1):116-121.**
16. **Karajannis MO, D; Filatov, A; Hagiwara, M; et al. Effects of everolimus on meningioma growth in patients with neurofibromatosis type 2 *Neuro-oncology.* 2014;16(suppl 5):Abstract AT-30.**
17. **Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. *Cancer cell.* Jul 2007;12(1):9-22.**
18. **Betz C, Hall MN. Where is mTOR and what is it doing there? *The Journal of cell biology.***

Nov 25 2013;203(4):563-574.

19. **Franz DN, Agricola KD, Tudor CA, Krueger DA. Everolimus for tumor recurrence after surgical resection for subependymal giant cell astrocytoma associated with tuberous sclerosis complex. *Journal of child neurology.* May 2013;28(5):602-607.**
20. **Choo AY, Yoon SO, Kim SG, Roux PP, Blenis J. Rapamycin differentially inhibits S6Ks and 4E-BP1 to mediate cell-type-specific repression of mRNA translation. *Proceedings of the National Academy of Sciences of the United States of America.* Nov 11 2008;105(45):17414-17419.**
21. **Choo AY, Blenis J. Not all substrates are treated equally: implications for mTOR, rapamycin-resistance and cancer therapy. *Cell cycle.* Feb 15 2009;8(4):567-572.**
22. **Wander SA, Hennessy BT, Slingerland JM. Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. *The Journal of clinical investigation.* Apr 2011;121(4):1231-1241.**
23. **Nelson V, Altman JK, Platanias LC. Next generation of mammalian target of rapamycin inhibitors for the treatment of cancer. *Expert opinion on investigational drugs.* Jun 2013;22(6):715-722.**
24. **James MF, Stivison E, Beauchamp R, et al. Regulation of mTOR complex 2 signaling in neurofibromatosis 2-deficient target cell types. *Molecular cancer research : MCR.* May 2012;10(5):649-659.**
25. **Zask A, Verheijen JC, Richard DJ. Recent advances in the discovery of small-molecule ATP competitive mTOR inhibitors: a patent review. *Expert opinion on therapeutic patents.* Jul 2011;21(7):1109-1127.**
26. **Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. *Nature reviews. Drug discovery.* Aug 2006;5(8):671-688.**
27. **Witzig TE, Geyer SM, Ghobrial I, et al. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 10 2005;23(23):5347-5356.**
28. **Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *The New England journal of medicine.* Feb 9 2012;366(6):520-529.**
29. **Cloughesy TF, Yoshimoto K, Nghiemphu P, et al. Antitumor activity of rapamycin in a Phase I trial for patients with recurrent PTEN-deficient glioblastoma. *PLoS medicine.* Jan 22 2008;5(1):e8.**
30. **James MF, Han S, Polizzano C, et al. NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth. *Molecular and cellular biology.* Aug 2009;29(15):4250-4261.**
31. **James MF, Stivison E, Beauchamp R, et al. Regulation of mTOR Complex 2 Signaling in Neurofibromatosis 2-Deficient Target Cell Types. *Mol Cancer Res.* May 2012;10(5):649-659.**
32. **Beauchamp RL, James MF, DeSouza PA, et al. A high-throughput kinome screen reveals serum/glucocorticoid-regulated kinase 1 as a therapeutic target for NF2-deficient meningiomas. *Oncotarget.* Jul 10 2015;6(19):16981-16997.**
33. **National Institutes of Health Consensus Development Conference Statement on Acoustic Neuroma, December 11-13, 1991. The Consensus Development Panel. *Archives of neurology.* Feb 1994;51(2):201-207.**
34. **Evans DG, Huson SM, Donnai D, et al. A clinical study of type 2 neurofibromatosis. *The Quarterly journal of medicine.* Aug 1992;84(304):603-618.**

35. **Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nature genetics.* Mar 2013;45(3):285-289.**

36. **Beauchamp RL, Banwell A, McNamara P, et al. Exon scanning of the entire *TSC2* gene for germline mutations in 40 unrelated patients with tuberous sclerosis. *Hum Mut.* 1998;12:408-416.**

37. **Jacoby LB, MacCollin M, Louis DN, al. e. Exon scanning for mutation of the *NF2* gene in schwannomas. *Hum. Mol. Genet.* 1994;3:413-419.**

38. **MacCollin M, Ramesh V, Jacoby LB, et al. Mutational analysis of patients with neurofibromatosis 2. *Am. J. Hum. Genet.* 1994;55:314-320.**

39. **Niida Y, Stemmer-Rachamimov AO, Logrip M, et al. Survey of somatic mutations in tuberous sclerosis complex (TSC) hamartomas suggests different genetic mechanisms for pathogenesis of TSC lesions. *Am J Hum Genet.* 2001;69(3):493-503.**

40. **Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, et al. Recommendations for imaging tumor response in neurofibromatosis clinical trials. *Neurology.* Nov 19 2013;81(21 Suppl 1):S33-40.**

41. **Fournier L, Ammari S, Thiam R, Cuenod CA. Imaging criteria for assessing tumour response: RECIST, mRECIST, Cheson. *Diagnostic and interventional imaging.* Jul-Aug 2014;95(7-8):689-703.**

42. **Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jul 1990;8(7):1277-1280.**

43. **Goutagny S, Bah AB, Henin D, et al. Long-term follow-up of 287 meningiomas in neurofibromatosis type 2 patients: clinical, radiological, and molecular features. *Neuro-oncology.* Aug 2012;14(8):1090-1096.**

44. **Ferner RE, Shaw A, Evans DG, et al. Longitudinal evaluation of quality of life in 288 patients with neurofibromatosis 2. *Journal of neurology.* May 2014;261(5):963-969.**

45. **Bloomer J, Derimanov G, Dumont E, Ellens H, Matheny C. Optimizing the in vitro and clinical assessment of drug interaction risk by understanding co-medications in patient populations. *Expert opinion on drug metabolism & toxicology.* Jun 2013;9(6):737-751.**

46. **University of Washington Metabolism and Transport Drug Interaction Database. 1999-2015; druginteractioninfo.org, 2016.**

47. **Federal Drug Administration Guidance for Industry. Drug-induced liver injury: Premarketing clinical evaluation. *Guidance for Industry* 2009; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf, 2016.**

48. **Thornton AR, Raffin MJ. Speech-discrimination scores modeled as a binomial variable. *Journal of speech and hearing research.* Sep 1978;21(3):507-518.**

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: INHIBITORS OR INDUCERS OF PERTINENT CYTOCHROME P450 PATHWAYS [45]

Potent or moderate inhibitors or inducers of CYP3A4/5:

Inhibitors (competitive)	**Inhibitors (time dependent)**	**Inducers**
Ketoconazole Itraconazole Indinavir Saquinovir Nelfinavir Atazanavir amprenavir fosamprenavir troleandomycin telithromycin fluconazole nefazodone cimetidine aprepitant miconazole fluvoxamine P-glycoprotein grapefruit juice[a] seville oranges[a] amiodarone[b]	erythromycin, clarithromycin, verapamil, ritonavir, diltiazem[c]	phenytoin rifampicin, St. John's Wort carbamazepine dexamethasone primidone griseofulvin carbamazepine barbiturate troglitazone pioglitazone oxcarbazepine nevirapine efavirenz rifabutin[d] phenobarbitone[e]

[a] 1 week minimum washout period
[b] 27 week minimum wash out period
[c] 2 week minimum washout period
[d] 3 week minimum washout period
[e] 5 week minimum washout period

** **Note**: unless specifically stated, 'within the appropriate wash-out period' refers to a minimum of 5x the reported elimination half-life, before the first dose of study treatment

Examples of in vivo substrates for OATP, and OCT drug transporters:

Transporter	**Substrate**
OATP	atorvastatin, bosentan, fexofenadine, glybutride, pitavastatin, pravastatin, **repaglinide**, rosuvastatin, simvastatin
OCT	Certirizine, dofetilide, gabapentin, metformin, **pilsicainide**, pindolol, **procainamide**, ranitidine, varenicline

Substrates in bold type have narrow therapeutic range

** **Note**: unless specifically stated, 'within the appropriate wash-out period' refers to a minimum of 5x the reported elimination half-life, before the first dose of study treatment

Examples of potent or moderate PGP (MDR1) and BRCP transporter enzyme inhibitors and inducers[45,46]

Transporter Enzymes	**Potent or moderate inhibitors/inducers**	
Pgp (MDR1) Potent inhibitors	None included on reference databases	
Pgp (MDR1) Moderate inhibitors	Dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, ritonavir, quinidine and verapamil vorapaxer	1 week 10 weeks
	Valspodar (PSC 833)	Half-life not found
Pgp (MDR1) potent inducers	None incuded on reference databases	
Pgp (MDR1) Moderate inducers	Carbamazepine and rifampin	3 weeks
BCRP Potent inhibitors	None included on reference databases	
BCRP Moderate inhibitors	Atazanavir, cyclosporine, lopinavir, ritonavir and tipranavir	1 week
BCRP inducers	None included on reference databases	

Definitions:

- Potent inhibitor (yielding AUC ratio ≥5)
- Moderate inhibitor (yielding AUC ratio ≥ 2 and <5)
- Potent inducers (AUC decreased by ≥ 80% or CL increased by more than 5fold (400%)
- Moderate inducers (AUC decreased by 50 - 80% or CL increased by more than 2-5 fold (100 - 400%)

APPENDIX C ACTIONS REQUIRED IN CASE OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction:
This appendix describes the process to be followed in order to identify and appropriately report cases of Hy'sLaw. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

As per FDA guidance, discontinuation of treatment and further evaluation of drug induced liver injury should be considered if not otherwise explained by underlying malignant disease:

ALT or AST >8xULN
ALT or AST >5xULN for more than 2 weeks
ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)

ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definition:

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.
For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's Law (PHL) cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative). The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see 13.2.2- Definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see 13.2.2- Definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow up:

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and assessment of Potential Hy's Law (PHL) cases

The instructions in this Section should be followed for all cases where PHL criteria are met.
No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director (MSD) and Global Safety Physician (GSP) will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below:

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

References

The above guidance is the main part of the Hy's law appendix. Further information, including additional sections that may be required for specific protocols, can be found in the FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'[47]

APPENDIX D: DRUGS THAT MAY AFFECT QT INTERVAL

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.

Drugs affecting QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD2014. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD2014 start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD2014 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 wee

APPENDIX F. NEUROFIBROMATOSIS 2 IMPACT ON QUALITY OF LIFE (NFTI-QOL) AND PENN ACOUSTIC NEUROMA-QUALITY OF LIFE (PAN-QOL) QUESTIONNAIRES

Neurofibromatosis 2 Impact on Quality of Life (NFTI-QOL) Questionnaire

INSTRUCTIONS FOR COMPLETING THE NFTI-QOL

Please complete the following information:

Age: _____ years

Gender: Male ☐ 1 Female ☐ 2 (please tick)

For each of the questions on the next page, please tick the one box that describes how you feel today

Usual activities include: work; housework; study; sport; social; family or leisure activities

Patient ID/Label:

Q1. Do balance or dizziness problems stop you performing your usual activities?

No balance problems or dizziness	☐0
Balance or dizziness problems but no difficulties	☐1
Balance or dizziness problems cause me some difficulties	☐2
Balance or dizziness problems stop my usual activities	☐3

Q2. Do hearing problems stop you performing your usual activities?

No hearing problems	☐0
Hearing problems but no difficulty	☐1
Hearing problems cause me some difficulty	☐2
Hearing problems stop my usual activities	☐3

Q3. Does facial weakness stop you performing your usual activities?

No facial weakness	☐0
Facial weakness, but no difficulty	☐1
Facial weakness causes some difficulty	☐2
Facial weakness stops my usual activities	☐3

Penn Acoustic Neuroma Quality of Life (PANQOL) Questionnaire

APPENDIX G. HEARING RESPONSE GUIDELINES

Clinical criteria for definition of hearing response based on a 50-word hearing test. Upper and lower limits for the 95% critical differences for percentage scores are adapted from Thornton.[48]

Baseline word recognition score (%)	95% critical difference (%)	Hearing Response (%)	Progressive hearing loss (%)
0	0–4	≥ 6	n/a
2	0–10	≥ 12	n/a
4	0–14	≥ 16	n/a
6	2–18	≥ 20	0
8	2–22	≥ 24	0
10	2–24	≥ 26	0
12	4–26	≥ 28	≤ 2
14	4–30	≥ 32	≤ 2
16	6–32	≥ 34	≤ 4
18	6–34	≥ 36	≤ 4
20	8–36	≥ 38	≤ 6
22	8–40	≥ 42	≤ 6
24	10–42	≥ 44	≤ 8
26	12–44	≥ 46	≤ 10
28	14–46	≥ 48	≤ 12
30	14–48	≥ 50	≤ 12
32	16–50	≥ 52	≤ 14
34	18–52	≥ 54	≤ 16
36	20–54	≥ 56	≤ 18
38	22–56	≥ 58	≤ 20
40	22–58	≥ 60	≤ 20
42	24–60	≥ 62	≤ 22
44	26–62	≥ 64	≤ 24
46	28–64	≥ 66	≤ 26
48	30–66	≥ 68	≤ 28
50	32–68	≥ 70	≤ 30
52	34–70	≥ 72	≤ 32
54	36–72	≥ 74	≤ 34
56	38–74	≥ 76	≤ 36
58	40–76	≥78	≤ 38
60	42–78	≥ 80	≤ 40
62	44–78	≥ 80	≤ 42
64	46–80	≥ 82	≤ 44
66	48–82	≥ 84	≤ 46
68	50–84	≥ 86	≤ 48
70	52–86	≥ 88	≤ 50

72	54–86	≥ 88	≤ 52
74	56–88	≥ 90	≤ 54
76	58–90	≥ 92	≤ 56
78	60–92	≥ 94	≤ 58
80	64–92	≥ 94	≤ 62
82	66–94	≥ 96	≤ 64
84	68–94	≥ 96	≤ 66
86	70–96	≥ 98	≤ 68
88	74–96	≥ 98	≤ 72
90	76–98	100	≤ 74
92	78–98	100	≤ 76
94	82–98	100	≤ 80
96	86–100	n/a	≤ 84
98	90–100	n/a	≤ 88
100	96–100	n/a	≤ 94

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09-6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR OFFICE USE	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant Study Drug Diary

Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol # _____
Your MD_____ Phone_____
Your RN_____ Phone_____

Study treatment instructions for AZD2014

Your dose of **AZD2014** is _____mg, made up of:
_____ **AZD2014** _____mg tablets and _____**AZD2014** _____mg tablets

- Please take the drug **twice daily on 2 consecutive days out of every seven days.** Permissible dosing days for AZD2014 are Monday/Tuesday, or Tuesday/Wednesday, or Wednesday/Thursday, Thursday/Friday, Friday/Saturday, Saturday/Sunday, or Sunday/Monday.
- Please take the pills at the **same time each day** (Approximately **12 hours apart**).
- After two hours a dose is considered "**missed**".
- You may take the dose up to **2 hours earlier** than the scheduled dose time, if need be.
- If you **vomit** within **30 minutes** after taking **AZD2014 or** later if the **tablet(s) can be identified** in the vomit content, then you can **re-take new tablet(s).**
- Pills **cannot** be crushed, chewed, or dissolved in water.
- You **can** take **AZD2014** with or without food.
- You **may** continue to drink **water** and you may take the pill with water.
- You should **avoid** eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, eg grapefruit juice or marmalade) **during this study. No more than** a small glass of grapefruit juice (120 mL) or half a grapefruit 1 to 2 teaspoons (15g) of Seville orange marmalade daily is **allowed.**
- Please bring this **diary** with you when you go to the clinic.
- Please store at **room temperature** (below 86 °F).

DOSING LOG

Drug: **AZD2014**
Permissible dosing days for AZD2014 are Monday/Tuesday, or Tuesday/Wednesday, or Wednesday/Thursday, Thursday/Friday, Friday/Saturday, Saturday/Sunday, or Sunday/Monday (two consecutive days each week). Please indicate the date, time, amount taken and any comments you may have.

Cycle _____

Doses	Date	Time	Number of pills taken	Comments
e.g. 1	10/12/2014	10 AM	3	Vomited pills
e.g. 2	10/12/2014	10 PM	3	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				