A pharmacodynamic pre-surgical study of Hedgehog pathway inhibition with LDE225 in men with high-risk localized prostate cancer

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List of abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
ALT	Alanine aminotransferase (glutamic pyruvic transaminase/SGPT)
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase (glutamic oxaloacetic transaminase/SGOT)
AUC	Area under the curve
BCC	Basal Cell Cancer
BCNS	Basal Cell Nevoid Syndrome
BCRP	Breast Cancer Resistance Protein
BID	bis in diem/twice a day
CK	Creatine Phosphokinase
Cmax	Maximum (peak) concentration of drug
Cmin	Minimum (peak) concentration of drug
CML	Chronic Myeloid Leukemia
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria Adverse Events
DLT	Dose Limiting Toxicity
DoR	Duration of tumor Response
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
EC	Ethics committee
ECG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
FAS	Full Analysis Set
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GPCR	G protein-couple receptor
Hgb	Hemoglobin
Hh	Hedgehog
H&N35	Head and Neck cancer module
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IHC	Immunohistochemistry
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety

IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate Dehyrogenase
LLOQ	Lower limit of quantification
MB	Medulloblastoma
MRI	Magnetic Resonance Imaging
MRP2	multi-resistance protein 2
NBCCS	Nevoid basal cell carcinoma syndrome
NMSC	Non-melanoma skin cancers
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PFS	Progression Free Survival
Pgp	P-glycoprotein
PHI	Patient Health information
PK	Pharmacokinetics
PMR	Partial Metabolic Response
PPS	Per-Protocol Set
PR	Partial Response
PTCH	Patched
QD	Quaque die/ once a day
QLQ-C30	Quality of Life Questionnaire
RP	Radical Prostatectomy
RAP	Report and Analysis Plan (RAP)
REB	Research Ethics Board
RECIST	Response Criteria in Solid Tumors
RT	Radiotherapy
RT-PCR	Real time PCR
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase (aspartate aminotransferase; AST)
SGPT	Serum glutamic pyruvic transaminase (alanine aminotransferase; ALT)
Smo	Smoothened
SSC	Study Steering Committee
TK	Toxicokinetics
TTR	Time to tumor response
Vss	Volume of distribution
WBC	White Blood cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study.
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1 Background

1.1 Overview of Prostate Cancer

Despite advances in the detection and treatment of prostate cancer, it remains the second most common cause of cancer-related deaths in the United States, killing approximately 30,000 men per year. Men with high-risk localized prostate cancer (Gleason sum 8-10, PSA >20 ng/mL, clinical stage ≥T3) account for the highest density of prostate cancer deaths and many succumb to their disease despite optimal local and systemic treatments (including surgery, adjuvant radiation therapy, androgen deprivation therapy, and chemotherapy), highlighting the need for novel prostate cancer therapies for these patients.

1.2 Overview of the Hedgehog (Hh) pathway and its role in cancer

Smoothened (Smo) is a G protein–coupled receptor (GPCR)–like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Normally, the activity of Smo is repressed by the trans-membrane receptor Patched (PTCH). Upon Hh ligand (Sonic Hh, Indian Hh or Desert Hh) binding to PTCH, its inhibitory effect on Smo is attenuated and the pathway becomes activated, leading to the release of Gli transcription factors from a complex of cytosolic inhibitory proteins. Active Gli transcription factors are translocated into the nucleus to induce Hh target genes, which control cell proliferation, survival and differentiation.

The Hh signaling pathway plays a critical role in the embryonic development and homeostasis of many human organs and tissues. Genetic alterations in the Hh pathway are linked to the development of several human tumors (basal cell carcinoma (BCC), medulloblastoma (MB) and rhabdomyosarcoma). Aberrant Hh signaling without evidence of genetic defects has also been linked with other tumors, such as pancreatic cancer, small cell lung cancer, gastro-intestinal tumors, ovarian cancer and prostate cancer. The pivotal role of Hh pathway in BCC was demonstrated in mice genetically engineered to express mutations of PTCH1 and SMO typically seen in human sporadic BCCs (Daya-Grosjean 2005).

1.2.1 Inhibition of Hh pathway by small molecules

The inhibition of the Hh signaling pathway as a therapeutic approach has increasingly become an area of extensive research. A number of small-molecule inhibitors of the Hh pathway, via smoothened inhibition, have progressed into clinical trials in a wide variety of cancers. Vismodegib (GDC0449; Roche) has being evaluated in clinical trials in basal cell carcinoma, medulloblastoma (recurrent and refractory in adults and young patients), ovarian cancer, advanced pancreatic cancer, advanced sarcoma, advanced breast cancer, advanced esophageal junction and SCLC. Vismodegib is now FDA-approved for use in patients with BCC. XL-139 (Bristol Myers-Squibb) is currently undergoing testing in combination with chemotherapy in SCLC, gastric/esophageal, multiple myeloma and chronic myeloid leukemia (CML). Recently, clinical trials have been initiated with PF-04449913 (Pfizer) and IPI 926 (Infinity) in combination in CML and in metastatic pancreatic cancer, respectively.

The anti-tumor activity of Smo inhibitors has recently been demonstrated in patients with locally advanced or metastatic BCC and recurrent medulloblastoma (von Hoff et al 2009, Scales and Sauvage 2009, Siu L EORTC-NCI-AACR 2009, Ahnert JR ASCO 2010, Ahnert

JR ESMO 2010, Rudin et al ESMO 2010) and in superficial BCC in patients with Gorlin syndrome (De Rie et al 2010). Vismodegib is now FDA-approved for patients with BCC including Gorlin syndrome.

1.3 Overview of LDE225 and Nonclinical studies

LDE225 is a potent selective and orally-bioavailable SMO antagonist from a novel structural class: N-[6-(cis-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)-1,1'-[biphenyl]-3-carboxamide diphosphate, currently being tested in clinical trials in patients with multiple types of cancer.

1.3.1 Pharmacodynamics

LDE225 potently inhibits both human and mouse Smo at low nanomolar concentrations (11 and 12 nM, respectively) in competitive binding *in vitro* assays. In a single dose pharmacokinetic–pharmacodynamic (PK-PD) study, 20 mg/kg LDE225 resulted in >90% inhibition Gli1 mRNA expression in tumor samples that was sustained for over 24 hrs. Daily multiple doses of LDE225 (20 mg/kg QD) caused >90% tumor regression in genetically defined *in vivo* MB xenograft models characterized by heterozygous deletion of PTCH.

1.3.2 Nonclinical pharmacokinetics and metabolism

LDE225 was well absorbed with good oral bioavailability, ranging from 68 to 100% in the mouse, rat, dog, and monkey after PO administration either in the form of a solution or a phosphate salt suspension. The compound showed low to moderate plasma clearance relative to blood flow in mouse, rat, dog and monkey. LDE225 exhibits high protein binding (approximately 98% in mouse, rat, dog and human plasma), independent of concentration. The compound was extensively distributed into tissues and its volume of distribution (V_{ss}) at steady-state was greater than total body water (1.9-7.0 L/kg). LDE225 exhibited high protein binding (approximately 98% in mouse, rat, dog and human plasma), independent of concentration. In rats, ~85% of LDE225 related radioactivity was eliminated into the feces, and renal excretion was minor, accounting for <3.0% of the administered dose.

Clearance of LDE225 is primarily hepatic by CYP3A4. LDE225 was extensively metabolized, with the major metabolic pathway being via mono- or di-oxygenation, demethylation, and oxidation leading to carboxylic acid formation, dealkylation, and dehydrogenation monohydroxylation. The elimination of metabolites is mainly through bile.

Studies with human liver microsomes demonstrated that LDE225 is a competitive inhibitor of CYP2B6 (IC_{50} 0.5 µM; K_i 0.045 µM), and CYP2C9 (IC_{50} 5 µM; K_i 1.7 µM), but showed very little or no inhibition of CYP1A2, 2A6, 2C8, 2C19, 2D6, 2E1 or 3A4/5 at concentrations of up to 100 µM. No apparent time-dependent inhibition of major CYP450 enzymes was observed. LDE225 is neither a substrate nor an inhibitor of P-glycoprotein (P-gp) or multi-resistance protein 2 (MRP2); but it has shown inhibitory effects on breast cancer resistance protein (BCRP), with an estimated IC_{50} value of 1.5 µM. The potential of LDE225 and its metabolites to undergo covalent binding to cellular macromolecules was found to be low.

The results of toxicokinetics (TK) studies with LDE225 indicated that systemic exposure after oral administration, as measured by C_{max} and AUC, was not linear and in general was less than dose-proportional in both rats and dogs. There was drug accumulation after once daily

repeat oral doses, which was more pronounced and dose-dependent in dogs. There was an apparent gender difference in exposure in rats following multiple dosing, with female rats exhibiting higher exposure than male rats. Please refer to the Investigator's Brochure for more details on the non-clinical toxicity, toxicokinetics and safety of LDE225.

1.3.3 Nonclinical toxicity and safety studies

The majority of adverse effects observed in toxicity studies in growing rats and dogs can be attributed to the pharmacologic action of LDE225, and the effects in both species were similar. The most striking effects of LDE225, which are consistent with literature reports on other Hh pathway inhibitors, were on bone and consisted of thinning or closure of growth plates in the sternum and femur and decreasing proliferating chondrocytes in the chostochondral junction of ribs. In addition, decreases in bone alkaline phosphatase were observed in dogs [Investigator Brochure]. The observations were more pronounced in rats, which is a species where the growth plate does not close. Similar observations have been reported for other Smo inhibitors in animal studies (e.g. Gli-Luc transgenic mice, IHH transgenic mice) including thinning and early closure of the growth plate, shortened bones, inhibition of tooth growth and abnormal bone structures, particularly the femur and tibia (Maeda 2007, Kimura 2008). This is likely due to the role of the Hh pathway in bone development, particularly in the early stages of bone formation and growth (Kimura 2008).

These effects are not likely to occur in the adult cancer patient population intended for the clinical studies due to the maturity of their skeletal system. However, it anticipated that Smo inhibition may likely affect the development of bones and teeth in growing children. Hence, monitoring for these effects will be required during therapy with Smo inhibitors in children. Preclinical cardiovascular safety pharmacology data do not indicate a clinical risk for QTc prolongation. There is also no indication of effects on the central nervous and respiratory systems from the preclinical data. Please refer to the Investigator's Brochure for more details on the non-clinical toxicity and safety of LDE225.

1.4 Clinical Experience with LDE225

1.4.1 Clinical safety and efficacy

LDE225 has been evaluated in a first-in-human, phase I, multicenter open-label dose-escalation study [CLDE225X2101] in patients with advanced solid tumors including medulloblastoma that have progressed despite standard treatments or have no existing therapies. The primary objective was to assess the safety, tolerability, PK, PD and potential efficacy of continuous once daily oral administration. The MTD for once daily administration of LDE225 was 800 mg. Data provided here are obtained from an active clinical trial database; therefore, they are preliminary and may be subject to change upon final QC review.

As of October, 2012, data were available on 103 patients with cancer who have been treated with LDE225 at dose levels of 100, 200, 400, 800, 1000, 1500, and 3000 mg once daily (QD) and 250, 400 and 750 mg twice daily (BID). Based on the available data, the recommended phase II dose of LDE225 in adults is 800 mg once daily.

DLTs that are characterized by CTCAE grade-3 or -4 increases in plasma creatinine phosphokinase (CK) were observed at once daily doses ≥800 mg and twice daily doses ≥250

mg (Table 1-1). The majority of the dose-limiting toxicity (DLT) events occurred during the initial 4-6 weeks of treatment with LDE225, except for three events that were observed after 6 weeks. None of the patients experienced impairment of renal function as a result of this toxicity. The DLTs resolved following discontinuation of LDE225 therapy.

Table 1-1 Incidence of dose limiting toxicities in Study CLDE225X2101

Dose of LDE225	No. of patients treated	Elevated plasma CK		
		No. patients with CTCAE grade-3	No. patients with CTCAE grade-4	Total (CTCAE grades 3 or 4)
100 mg QD	6	0	0	0
200 mg QD	6	0	0	0
400 mg QD	5	0	0	0
800 mg QD	26	1	1	2
1000 mg QD	11	1	1	2
1500 mg QD	9	0	3	3
3000 mg QD	10	0	3	3
250 mg BID	14	1	1	2
400 mg BID	8	1	1	2
750 mg BID	8	0	5	5
Total	103	4	15	19

Across all the doses studied, commonly reported CTCAE grade-1 or -2 (in >10% of patients) that are suspected to be treatment-related include: nausea, vomiting, dysgeusia, decreased appetite, myalgia, muscle spasms, increased blood CK, alopecia, asthenia and fatigue (see Table 1-2). No treatment-related clinically significant changes in the other safety laboratory data (hematology, and urinalysis), vital signs or ECGs have been observed for any of the patients treated in the study. Refer to LDE225 Investigator's Brochure for further details.

Table 1-2 Adverse events suspected to be related with LDE225, occurring in ≥5% of patients in Study CLDE225X2101 as of October 2012

	800 mg QD* (n=26)		All doses** (n=103)	
	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)
Nausea	3 (11.5)		26 (25.2)	
Dysgeusia	5 (19.2)		29 (28.2)	
Weight decrease	4 (15.4)		10 (9.7)	
Decreased appetite	4 (15.4)		18 (17.5)	
Vomiting	2 (7.7)		13 (12.6)	
Diarrhea	2 (7.7)		7 (6.8)	
Constipation	1 (3.8)		6 (5.8)	
Muscle spasms	9 (34.6)		31 (30.1)	
Myalgia	5 (19.2)		18 (17.5)	1 (1.0)
Blood CK increased	6 (23.1)	2 (7.7)	30 (29.1)	19 (18.4)
AST increased	1 (3.8)		8 (7.8)	3 (2.9)
ALT increased	1 (3.8)		7 (6.8)	3 (2.9)
Fatigue	1 (3.8)		15 (14.6)	
Asthenia	5 (19.2)	1 (3.8)	11 (10.7)	2 (1.9)
Alopecia	3 (11.5)		11 (10.7)	
Lethargy	3 (11.5)		7 (6.8)	

* Recommended phase II dose in adults ** All doses, including BID and QD schedule

1.4.1.1 Clinical efficacy

Preliminary antitumor activity and evidence of disease stabilization has been observed with LDE225 treatment. Nine (9) adult patients with recurrent MB have been treated in the phase I study CLDE225X2101. Of these, three (3) patients achieved confirmed partial tumor responses at 200 mg QD (by RECIST), 800 mg QD (by RECIST) and 1500 mg QD (by FDG-PET) and remained on treatment for approximately 6, 8 and 10 months, respectively. The remaining patients progressed after 1 to 4 months on study therapy (see Table 1-3).

Table 1-3 Antitumor activity in adult patients with recurrent medulloblastoma

Patient	Dose	Overall Best Response	Time on Study* (months)
0502-00103	100 mg QD	PD	1.0
0001-00103	200 mg QD	PR	6.0
0502-00104	200 mg QD	PD	2.0
0502-00121	800 mg QD	SD	4.0
0010-00111	800 mg QD	PR	9.0
0001-00134	800 mg QD	PD	2.5
0501-00113	1500 mg QD	PD	2.0
0001-00113	1500 mg QD	PMR	10 .0
0502-00125	250 mg BID	PD	2 .0

PD, disease progression; PMR partial metabolic response; PR, partial response; SD, stable disease

* Time from trial entry until documented disease progression. All the MB patients are off study

A total of 16 patients with locally advanced/metastatic BCC were enrolled. Table 1-4 shows the antitumor activity observed in 10 patients who received LDE225 therapy for >2 months.

Table 1-4 Antitumor activity in patients with BCC

Patient	Dose	Overall best response	Approximate time on study in (months)
502-0102	100 mg QD	SD	32*
001-0127	800 mg QD	SD	9
001-0131	800 mg QD	SD	6
001-0137	800 mg QD	PR	7*
020-0103	800 mg QD	PR	7
502-0119	800 mg QD	PR	17*
020-0110	1000 mg QD	PR	15*
020-0112	250 mg BID	SD	7
001-0139	250 mg BID	PR	7*
001-0119	400 mg BID	CR	15

CR, complete response; PR, partial response; SD, stable disease; PD, disease progression

* Patients still on therapy

1.4.2 Clinical pharmacokinetics and pharmacodynamics

The preliminary pharmacokinetics (PK) data from the ongoing phase 1 study in patients with advanced solid tumors [CLDE225X2101] showed that the median time of C_{max} (T_{max}) occurs 2-13 hours (range: 1-48 hours) after oral dosing. Plasma exposure to LDE225 (C_{max} and

$AUC_{0\text{-}168h}$) after single dose administration increased dose proportionally from 100 to 400 mg and less than dose-proportionally above 400 mg. After repeated once-daily (QD) dosing from 100 mg to 3000 mg, C_{max} and $AUC_{0\text{-}24h}$ on Cycle 1 Day 15 increased approximately dose-proportionally up to 400 mg and less than dose proportionally above 400 mg. After twice-daily (BID) administration of LDE225 from 250 mg to 750 mg, Cmax and $AUC_{0\text{-}12h}$ on Cycle 1 Day 15 also increased approximately dose-proportionally in this dose range. BID dosing results in higher systemic exposures compared with the equivalent once daily regimen. The 7-day PK run-in phase implemented in this phase 1 study was not long enough to allow for accurate estimation of the half-life using non-compartmental methods. Based on available data as of December 8, 2011, steady-state was achieved in a limited number of patients, after 2 weeks to 6 cycles of repeated dosing with an accumulation ratio of 6- to 90-fold based on Cmin. The estimated effective half-life, calculated based on the C_{min} accumulation from these patients, ranged from 4 days to 62 days (median 19 days). The inter-subject coefficient of variation for Day 15 AUC and C_{max} is 33 to 106% and 39 to 113%, respectively, across the dose range of 100 mg to 3000 mg/day. At the recommended phase II dose of 800 mg QD, the inter-subject coefficient of variation for Day 15 $AUC_{0\text{-}24h}$ and C_{max} is 50.0% and 54.5%, in 18 and 20 subjects, respectively. Exploratory analyses suggested that the incidence of CK DLT increased with both AUC and C_{max} on day 15.

Analyses of skin punch biopsies taken at baseline and at the end of the first treatment cycle have shown evidence of potent target modulation, as measured by Gli1 mRNA, in a dose- and exposure (C_{min})-dependent manner. The available data shows that LDE225 caused ≥95% mean reduction in Gli1 expression in skin compared with baseline values. The maximum observed inhibition of the target in skin (as measured by Gli1 expression) was observed at 750 mg BID (see Table 1-5).

Table 1-5 Inhibition of Gli1 mRNA expression in skin

Dose	N	Mean Fold change	95 % CI (Lower, Upper)	Mean % Inhibition
100 mg QD	4	-1.7	-6.4, 4.9	39.6%
200 mg QD	4	-4.1	-11.4, 1.1	75.6%
400 mg QD	3	-9.2	-53.5, -1.0	89.1%
800 mg QD	20	-3.8	-6.6, -2.2	73.5%
1000 mg QD	6	-5.7	-20.8, -1.5	82.3%
1500 mg QD	5	-17.5	-30.4, -8.2	94.3%
3000 mg QD	4	-13.9	-27.0, -6.0	92.8%
250 mg BID	7	-7.4	-12.7, -4.3	86.5 %
400 mg BID	7	-6.4	-11.2, -3.7	84.4%
750 mg BID	6	-26.5	-45.7, -15.3	96.2%

1.5 Study purpose and rationale

Discrepancies between preclinical data and clinical observations highlights the need to carry out pharmacodynamic studies of promising cellular pathway inhibitors before conducting large-scale clinical trials for efficacy. While pre-clinical data suggests a role for LDE225 in the inhibition of prostate cancer progression, no clinical study exists which confirms the ability of LDE225 to suppress the Hedgehog pathway in prostate cancer cells (or benign prostate tissue).

From a tissue acquisition perspective, the presurgical setting is ideal for the study of novel drug effects on both normal and neoplastic prostate tissues. In addition, our data (and that of other investigators) suggest that the Hedgehog pathway is active in men with high-risk localized prostate cancer and thus this cohort represents an appropriate population for study of Hh pathway inhibitors. Specifically, previous work has suggested that pathways characteristic of metastatic disease might be active in high-grade localized tumors (Ross et al. 2011). Expanding on this work, we characterized gene expression profiles from tumors of clinically and pathologically matched men with localized high-grade disease who had no preoperative treatment and either experienced rapid metastasis following extirpative surgery or no metastases for a 5-year period. Analysis of functional annotation of differentially expressed genes in these two groups demonstrated enrichment for embryonic stem cell pathways among the localized tumors of men who would experience metastasis (adjusted $P<0.0001$) and a 3.7-fold increase in Sonic Hh expression in these tumors (adjusted $P<0.035$). These data and that of others suggest up-regulation of Hh signaling in localized prostate cancer with metastatic potential (Tzelepi et al. 2011, Chen et al. 2010, Kim et al. 2011).

We believe that completion of this pharmacodynamic (pre-surgical) trial will guide future use of LDE225 in prostate cancer. Furthermore, knowledge of molecular responses to Hedgehog signaling inhibition in prostate cancer could help better select patients and the timing for treatment with LDE225 or with combination therapies.

2 Objectives and Endpoints

We propose to determine the effects of LDE225 on neoplastic prostate tissue from men at high risk of systemic disease progression, by comparing pre-surgical core-biopsy specimens to tumor tissue harvested at the time of prostatectomy. In addition to assaying drug-related on-target effects (i.e. *GLI* expression changes) we propose to determine the effects of Smo inhibition on the prostate cancer transcriptome.

Primary Objective

(1) To determine the pharmacodynamic (PD) effects of LDE225 on resected prostate tissue from men undergoing radical prostatectomy for high-risk localized prostate cancer (as measured by reductions in *Gli1* mRNA expression).

Secondary Objectives

(1) To determine whether presurgical treatment with LDE225 can exert a pathological effect on high-risk tumors (*i.e.* increase apoptosis, decrease proliferation).

(2) To evaluate whether presurgical treatment with LDE225 diminishes the risk of PSA recurrence following prostatectomy.

(3) To evaluate the safety and tolerability of LDE225 in the presurgical setting.

Exploratory Objectives

(1) To evaluate genome-wide mRNA expression changes in prostate cancer induced by LDE225 exposure.

The objectives and related endpoints are summarized in the Table below.

	Objective	Endpoint	Analysis
Primary	Pharmacodynamic effect of LDE225 on prostate tissue	50% reduction in *Gli1* mRNA expression comparing pre-operative prostate biopsies to radical prostatectomy specimens	qRT-PCR performed on pre-operative tumor biopsy specimens and tumor from RP specimens. Comparison performed within and between treated and untreated groups. Correlation of *Gli1* levels to pre-operative *Gli1* expression.
Secondary	-Pathological effect on localized high-risk cancer	-Assessment of tumor stage and grade (predicted versus actual) and changes in proliferation and apoptosis	-Routine pathologic analysis. Additionally, semi-quantitative IHC for Ki-67 and cleaved caspase-3. Comparison performed within and between treated and untreated groups.
	-To determine whether pre-surgical treatment with LDE225 diminishes the risk of PSA recurrence following prostatectomy	-PSA $\geq$0.2 ng/ml at 3 months following prostatectomy	-Routine serum ELISA for PSA
	-To evaluate drug-related toxicities including peri-operative complications	-Length of surgery, intraoperative blood loss, length of hospital stay, rates of post-operative complications (infection, wound breakdown, deep vein thrombosis, within 90 days from surgery)	-Comparison of routinely collected intraoperative and post-operative data between treated and untreated groups
Exploratory	Evaluate genome-wide mRNA expression changes in prostate cancer induced by LDE225 exposure	Gene expression analysis on biopsy and prostatectomy tissue using the Affymetrix GeneChip Human Exon 1.0ST Array	Differential gene expression analysis and analysis of functional annotation comparing biopsy and prostatectomy specimens both between and within groups

3 Investigational Plan

3.1 Overview and study design

This pharmacodynamic/phase 0 trial is designed as a randomized two-arm (LDE225 vs. observation groups) open-label prospective clinical trial in men with localized high-risk prostate cancer undergoing radical prostatectomy.

Activation of the Hedgehog pathway is most reliably indicated by increased expression of the *GLI1* transcription factor. Quantitiative RT-PCR (qRT-PCR) provides the most reliable means to assess changes in *GLI1* expression upon exposure to drug and will be used as our primary readout. Our intent will be to examine the fold change in *GLI1* expression in each man following exposure to drug (comparing pre-operative needle biopsy tissue to surgical tissue obtained from the same man's prostatectomy specimen). Because the effects of surgery and fluctuations in hedgehog signaling in the prostate are unknown, *GLI1* expression will also be compared between biopsies and prostatectomy specimens for men without drug exposure. As treatment with LDE225 may alter the gene expression of other Hedgehog pathway members and affect separate signaling pathways, as an exploratory goal, we will perform genome-wide expression analysis using the GeneChip Human Exon 1.0ST Array (Affymetrix) and will confirm fluctuations in selected genes of interest.

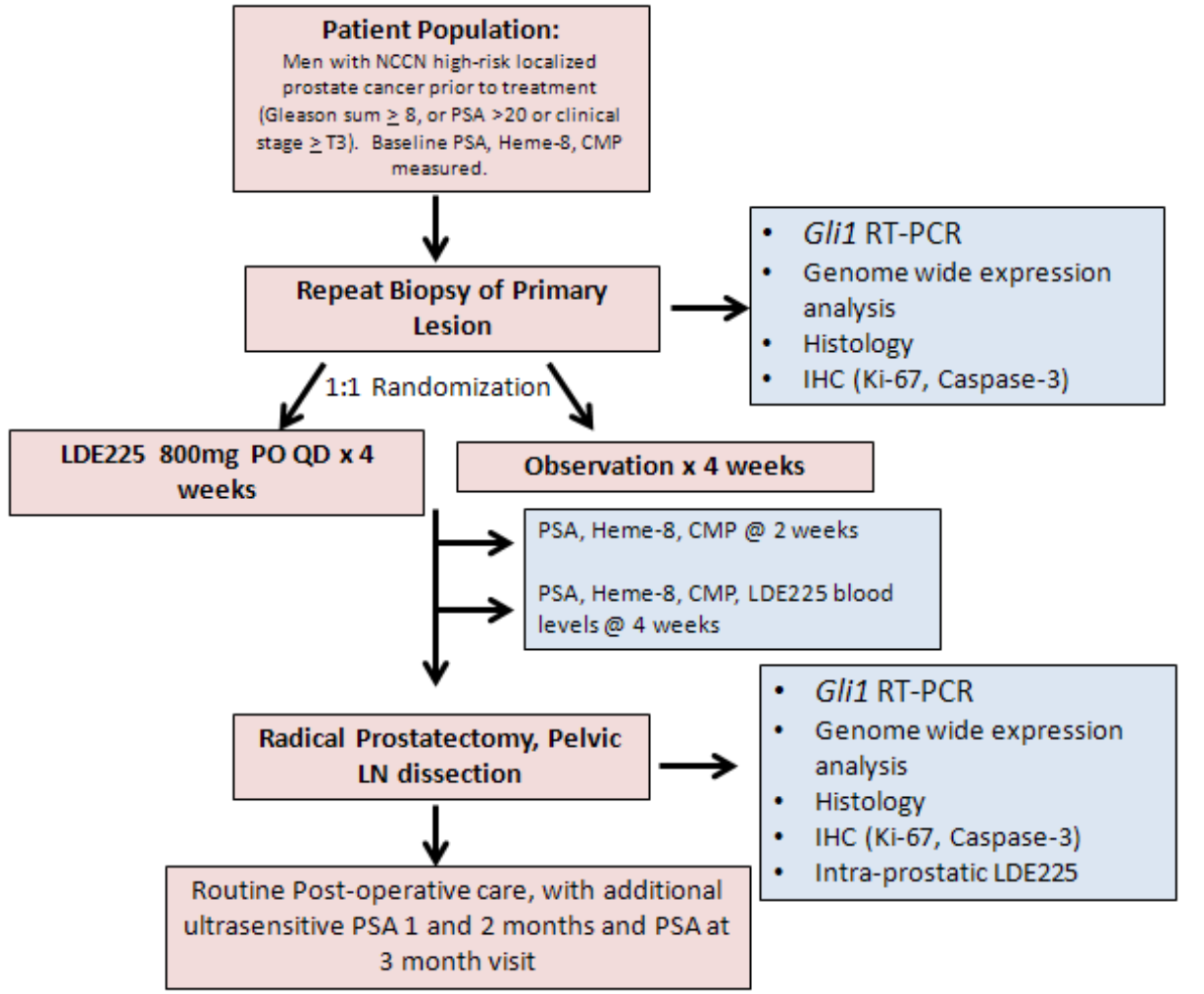
High-risk patients will be identified based on their core-needle biopsy features, PSA levels, and clinical stage. Eligible men (NCCN high-risk (Gleason sum $\geq$8, or PSA >20 or clinical stage $\geq$T3 with no evidence of metastatic disease) will undergo a repeat prostate biopsy at Johns Hopkins with multiple (up to 12) cores taken from the area of their primary lesion. This tissue will be frozen fresh and used for analysis of *Gli1* mRNA expression and array analysis as well as mounted for pathological analysis and IHC analysis of proliferation (Ki-67) and apoptosis (cleaved caspase-3) markers.

After obtaining baseline laboratory and clinical values (including an ECG, PSA, hematologic, and renal and hepatic panels), men will receive oral LDE225 800 mg/day or observation daily for 4 weeks (±3 days) prior to prostatectomy. Patients will have a clinical visit and an ECG and laboratory testing will be performed at 2 weeks and then again at 4 weeks, including a 4-week pre-prostatectomy measurement of PSA and a blood sample to determine plasma LDE225 levels by LC-MS/MS. Previous studies using other oral Hedgehog inhibitors indicate that 4 weeks will allow time for steady-state levels of drug in the plasma and for inhibition of *Gli1* expression (LoRusso et al. 2011).

Men will undergo radical prostatectomy (with bilateral pelvic lymphadenectomy as appropriate), at which point two 250-mg biopsies of prostate tissue will be obtained, frozen and stored for analysis (including *Gli1* expression, genome-wide expression analysis, intra-prostatic LDE225 levels, Ki-67, and cleaved caspase-3*)* with the remainder of the prostate tissue then being formalin-fixed paraffin-embedded (FFPE) and cross-sectioned for analysis as per our standard institutional procedures.

Relative fold-changes in mRNA expression of *Gli1* will be determined by first normalizing input amounts of the preoperative biopsy and prostatectomy biopsies to the housekeeping gene *HPRT1*. IHC comparisons between diagnostic biopsy specimens and prostatectomy specimens will be made by calculating immunoreactivity scores (staining intensity × percentage cell involvement).

All men will receive routine post-operative care, and in addition will have ultrasensitive PSA testing at 1 and 2 months post-op followed by standard PSA testing at the 3 month visit.



Study Schema

3.1.1 Investigational treatment

The investigational study drug used in this trial is LDE225, which is supplied as oral capsules.

3.1.2 Treatment arms

This will be a randomized 2-arm trial. Arm 1 will receive LDE225 by mouth 800 mg daily for 4 weeks (± 3 days); Arm 2 will receive no treatment (observation) prior to prostatectomy.

3.1.3 Treatment duration

Patients will continue on LDE225 therapy for 4 weeks (±3 days) in Arm 1, or until they experience a treatment toxicity requiring discontinuation.

3.1.4 Treatment assignment/randomization

Patients will be randomized (1:1) to treatment with LDE225 or observation, with a total sample size of 22 patients (*i.e.* 11 per group).

3.2 Rationale for the study design

Discrepancies between preclinical data and clinical observations highlight the need to carry out pharmacodynamic studies of promising cellular pathway inhibitors before conducting large-scale clinical trials for efficacy. While pre-clinical data suggests a role for LDE225 in the inhibition of prostate cancer progression, no clinical study exists which confirms the ability of LDE225 to suppress the Hedgehog pathway in prostate cancer. For this reason, we believe that a phase 0 (pharmacodynamic) trial would be instrumental in determining whether further larger clinical studies should be carried out with LDE225 in prostate cancer.

From a tissue acquisition perspective, a pre-surgical trial involving biopsy tissue collection and tissue at prostatectomy would be ideal for determining whether LDE225 has effects on its *in vivo* target and additionally to measure genome-wide alterations caused by drug exposure.

Based on our pre-clinical data (and that of other groups) we believe that men with NCCN high risk prostate cancer are the best candidates for this trial due to relative enrichment in baseline Hedgehog pathway activation in this subgroup (Ross et al. 2011, Tzelepi et al. 2011, Chen et al. 2010, Kim et al. 2011). Because the temporal variability of Hedgehog pathway activity and the effects of surgical treatment on pathway activation are largely unknown, we believe that a control/observation arm is critical to the study.

4 Population and Eligibility Criteria

Target Population. This study will include men age 18 or older diagnosed with NCCN high-risk (Gleason sum ≥8, or PSA >20, or clinical stage ≥T3) prostate cancer who are candidates for radical retropubic prostatectomy.

4.1 Inclusion criteria

Patients must meet **all** of the following criteria:

1. Provide written informed consent prior to any screening procedures.
2. Age 18 years or older.
3. Histologically-documented prostatic adenocarcinoma in ≥2 cores
4. ECOG performance status ≤2
5. Localized prostate cancer with *at least one* of the following NCCN high-risk features:
   - Gleason sum ≥8
   - PSA >20 ng/mL
   - Clinical stage ≥T3
6. Must be a candidate for radical prostatectomy
7. No evidence of known metastatic disease (M0 or Mx allowed)
8. Adequate bone marrow, liver and renal function as specified below:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Hemoglobin (Hgb) ≥ 9.0 g/dL
- Platelets ≥ 100 x 10^9/L
- Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal)
- AST and ALT ≤ 2.5 x ULN
- Plasma creatine phosphokinase (CK) < 1.5 x ULN, if known
- Serum creatinine ≤ 1.5 x ULN [or 24-hour creatinine clearance ≥ 50ml/min]

9. Patient is able to swallow and retain oral medications

4.2 Exclusion criteria

Patients must not meet **any** of the following criteria:

1. Patients who have had major surgery within 4 weeks of enrollment.
2. Patients with concurrent uncontrolled medical conditions that may interfere with their participation in the study.
3. Patients unable to take oral drugs (*e.g.* lack of physical integrity of the upper GI tract or known malabsorption syndromes).
4. Patients who have previously been treated with LDE225 or other Hh pathway inhibitors.
5. Patients who have neuromuscular or muscular disorders (*e.g.* inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are known to cause rhabdomyolysis (such as statins and fibrates), and that cannot be discontinued at least 2 weeks prior to starting LDE225. If it is essential that the patient stays on a statin for hyperlipidemia, only *pravastatin* may be used with extra caution. Patients should not plan to embark on a new strenuous exercise regimen after initiation of study treatment. (NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided whilst on LDE225 treatment).
6. Patients who have taken part in an experimental drug study within 4 weeks or 5 half-lives (whichever is longer) of initiating treatment with LDE225.
7. Patients who are receiving other anti-neoplastic therapy (*e.g.* chemotherapy, targeted therapy or radiotherapy) concurrently or within 2 weeks of starting LDE225.
8. Patients taking moderate/strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with LDE225. Medications that are strong CYP3A4/5 inhibitors should be discontinued for at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with LDE225.
9. No concurrent use of statins (except for pravastatin, *if absolutely necessary*)
10. No concurrent warfarin or Coumadin-derivatives
11. Impaired cardiac function or significant heart disease, including any one of the following:
    - Angina pectoris within 3 months
    - Acute myocardial infarction within 3 months
    - QTc >450 msec on the screening ECG
    - A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome

- Other clinically significant heart disease (*e.g.* heart failure, uncontrolled/labile hypertension, or history of poor compliance with an antihypertensive regimen)

12. Patients who are not willing to apply highly effective contraception during the study and through the duration of LDE225 treatment.
    - **Male patients** must use highly effective (double barrier) methods of contraception (*e.g.*, spermicidal gel plus condom) for the entire duration of the study, and continuing using contraception and refrain from fathering a child for 6 months following the last dose of the study drug. A condom is also required to be used by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the study treatment via seminal fluid. Sexually active males must be willing to use a condom during intercourse while taking the study drug and for 6 months after stopping investigational medications and agree not to father a child during this period.
13. Patients unwilling or unable to comply with the research protocol.

5 Treatment

5.1 Treating the patient

The treating investigator needs to instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded in the dosage administration record (CRF) as appropriate.

5.1.1 Administration

Table Treatment and schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or regimen
LDE225	Capsules (200 mg) for oral use	800 mg	Daily

LDE225 will be administered orally, on a continuous once-daily schedule, at a dose of 800 mg. Participating patients will receive flat doses on mg/day basis and not according to their body weight or body surface area. LDE225 is supplied as 200-mg hard gelatin capsules in bottles and must be stored at 2-8°C/ 35.6-46.3°F. **Patients will receive 4 capsules of LDE225 daily (= 800 mg/day)**.

5.1.2 Dosing and treatment schedule

Patients will be dosed at 800 mg of LDE225 daily. Hard gelatin capsules at 200 mg are available (4 capsules will be taken all at one time). Dose escalation will *not* be allowed.

LDE225 should be taken as follows:

- Men should be instructed to take their daily dose at approximately the same time each day
- On days where PK samples need to be collected prior to taking study drug, that day's dose should be taken in the clinic (study site)
- Each daily dose of LDE225 should be taken with a glass of water and consumed over as short a time as possible (*e.g.* 1 capsule every 2 minutes)

- Patients should be instructed to swallow capsules whole and to *not chew or open* capsules
- Each daily dose of LDE225 (including days which involve PK blood sampling) should be taken **2 hours after** a light breakfast (*e.g.,* consisting of juice, toast and jam). Food intake should be avoided for at least 1 hour after study drug administration
- Patients must avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during the entire study. The juices and products containing these fruits may also be avoided.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose the following day
- If the patient forgets to take his daily morning dose, then he should take LDE225 within 6 hours after the missed dose. If more than 6 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose
- Patients should inform the investigational site staff of any missed or delayed doses

5.1.3 Dose modification and dose delay

Investigators should follow the guidelines *described below* for the modification of LDE225 treatment. Any plan to deviate from these guidelines in view of the patient safety must be previously discussed with Novartis unless there is an urgent need for action.

All dose modifications should be based on the worst preceding toxicity. If study treatment is being held due to toxicity, scheduled visits and all assessments should continue to occur except the dosing of the study drug. Treatment related toxicities are adverse events that are possibly, probably or definitely related to the study drug.

Any grade 3 or grade 4 toxicities will result in discontinuation of the study drug. Men with prolonged grade 2 toxicity will receive a reduced dose of the study drug at 400mg. If the grade 2 toxicitiy continues on the reduced dose then the dose level will be reduced again to 200mg. A maximum of two dose-reduction steps will be allowed (see Table below), after which the patient will be discontinued from study treatment.
For patients who undergo dose interruptions (delays), if the same toxicity returns after re-initiation of treatment, regardless of duration, the second re-initiation must resume at a lower dose. If the patient requires a dose interruption of >7 days from the previous dose, then the patient must be discontinued from study treatment although he may still undergo prostatectomy. Patients who discontinue the treatment due to an adverse event or an abnormal laboratory value must be followed until resolution or stabilization of the event.

All dose changes or interruptions must be recorded in the dosage administration record (CRF) as appropriate.

Table Dose reductions for LDE225

Dose reduction*			
	Starting dose level	Dose level -1	Dose level -2
LDE225 dose (mg QD)	800	400	200
*Dose reduction should be based on the worst toxicity demonstrated.			

Detailed indications and instructions for dose-modifications are shown below in Table 5-3. Different dose modifications are dependent on the type and severity of the toxicity, as shown in Table 5-3.

Table 5-1 Recommended Dose Modifications and Dose Delays for suspected treatment-related toxicities

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
<u>Hematologic</u>	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Reduce dose to 400mg. If resolved in ≤ 7 days then maintain dose level. If not resolved in ≤ then decrease level to 200mg
Grade 3 or 4 (ANC < 1000 - 500/mm^3 or < 500/mm^3)	• Discontinuation of study drug
Thrombocytopenia (PLT)	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Reduce dose to 400mg. If resolved in ≤ 7 days then maintain dose level. If not resolved in ≤ then decrease level to 200mg
Grade 3 or 4 (PLT < 50,000 - 25,000/mm^3 or < 25,000/mm^3)	• Discontinuation of study drug
Febrile Neutropenia	
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then decrease dose by 1 step
<u>Muscle Toxicity</u>	
Elevated creatine phosphokinase (CK)	
Asymptomatic (no new-onset muscle pain/spasm or worsening of pre-existing muscle pain/spasm) CTCAE grade 1 or 2 CK elevation	• For CTCAE grade 1 CK elevation, continue treatment on same dose and continue monitoring as per schedule of assessments • For sites in France: For treatment-emergent CTCAE grade 1 CK elevation, continue treatment on same dose. CK should be measured weekly until CK returns to normal for baseline value. • For CTCAE grade 2 CK elevation, collect blood sample for PK and consider performing a muscle biopsy; continue on same dose level of LDE225. CK should be measured weekly until resolution to ≤ grade 1.
Symptomatic (new-onset or worsening of pre-existing muscle pain/spasm) with CTCAE grade 1 or 2 CK elevation	• For CTCAE grade 1 CK with muscle pain/spasm ≥ CTCAE grade 1, continue treatment at same dose and measure CK weekly until CK returns to normal or baseline value or muscle pain/spasm resolves • For CTCAE grade 2 CK with muscle pain/spasm ≥ CTCAE grade 1, collect blood sample for PK and continue treatment at same dose level of LDE225. CK should be measured weekly until CK is ≤ CTCAE grade 1

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
CTCAE grade 3 or 4 CK elevation (with or without muscle pain/spasm)	• Discontinuation of study drug
Muscle pain/spasm (new onset or worsening of pre-existing muscle pain/spasm)	• For CTCAE grade 1 muscle pain/spasm, continue treatment on the same dose and planned assessments • For CTCAE ≥ grade 2 muscle pain/spasm, measure CK weekly until muscle pain resolves to ≤ grade 1. If CK is elevated, follow guidance for CK elevation as described above. Continue treatment with LDE225 • For new-onset CTCAE grade 3 muscle pain/spasm, study drug will be discontinued
<u>Renal</u>	
Serum creatinine	
Serum creatinine <1.5 x ULN	Maintain dose level
Serum creatinine 1.5-3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step (consider checking serum CK, if not already done)
Grade 3 Serum creatinine > 3.0 - 6.0 x ULN	Discontinuation of study drug
Grade 4 Serum creatinine > 6.0 x ULN	Discontinuation of study drug
<u>Hepatic</u>	
Bilirubin	
Total bilirubin <1.5 x ULN	Maintain dose level
Total bilirubin 1.5-3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease by 1 step
Grade 3 Total bilirubin > 3.0 - 10.0 x ULN	Discontinuation of study drug
Grade 4 Total bilirubin > 10.0 x ULN	Discontinuation of study drug
AST or ALT	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	• Discontinuation of study drug
Grade 4 (> 20.0 x ULN)	Discontinuation of study drug

Recommended dose modifications for LDE225**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Cardiac	
Cardiac - prolonged QTc interval ≥ grade 3 (QTc >500 msec or >60 ms from baseline on at least 2 separate ECGs taken within 1 hour)	**First Occurrence:** • Omit dose • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTc >500 ms • If QTc remains > 500 ms, repeat ECG as clinically indicated but at least once a day until the QTc returns to <480 ms. • Once QTc prolongation has resolved, study treatment may be restarted at a reduced dose level **Second Occurrence:** • discontinue patient from further study treatment
Cardiac, general	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinuation of study drug
Grade 4	Discontinuation of study drug
Other adverse events**	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinuation of study drug
Grade 4	Discontinuation of study drug
All dose modifications should be based on the worst preceding toxicity. Treatment related toxicities are adverse events that are possibly, probably or definitely related to the study drug.	
If the dose-limiting toxicity recurs in a patient following 2 dose reductions, then further therapy with LDE225 will not be continued.	
If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose because of an LDE225-related toxicity, then the patient must be discontinued from the study.	
*Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0).	
** If the investigator deems that a recommended dose reduction or the recommendation to maintain the same dose level is not in the best interest of the patient, this decision may be discussed with Novartis on a case-by-case basis.	

5.1.4 Protocol Stopping Rules

The study will be closed if >3 patients experience a delay in surgery by more than 2 weeks due to drug related toxicities. In other words, if 4 or more patients in the experimental arm have their prostatectomy delayed by more than 2 weeks, we will close the study. In addition, the study will close if we observe >3 patients who experience a grade 3 or grade 4 adverse event that is possibly, probably or definitely related to the study drug. In other words, if 4 or more patients in the experimental arm experience a grade 3 or grade 4 drug-related toxicity the study will be closed.

5.1.5 Permitted concomitant therapy

Medications required to treat adverse events and manage cancer symptoms, concurrent stable disease (*e.g.,* controlled hypertension) and supportive care agents such as erythropoietin, granulocyte growth factors, or blood transfusion, and pain medications are allowed. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study medication. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the CRF.

5.1.6 Permitted concomitant therapy requiring caution and/or action

LDE225 is an inhibitor of breast cancer resistance protein (BCRP) *in vitro*. Therefore substrates, especially those with a narrow therapeutic range, should be used with caution. BCRP substrates include zidovudine, pantoprazole, cimetidine, sulfasalazine, nitrofuratoin, mitoxantrone, methotrexate, topotecan, imatinib, and irinotecan. *However, the use of statins is generally prohibited during this study (except for pravastatin).*

In vitro drug metabolism studies reveal that the metabolism of LDE225 is mediated by CYP3A4 and also a potent inhibitor of CYP2C9 and CYP2B6. Clinical studies have not yet been performed to confirm the potential effect of LDE225 on substrates drugs metabolized by CYP2C9 in patients. Also, it is not known the potential effect of low and moderate CYP3A4 inhibitors and inducers on LDE225 clearance. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP2C9 and CYP2B6, except drugs which have narrow therapeutic index/sensitive substrates for these two isoforms and statins. Caution is advised when LDE225 is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment.

5.1.7 Prohibited concomitant therapy

5.1.7.1 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, immunotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the treatment portion of the study.

5.1.7.2 Strong CYP3A inhibitors and inducers

No clinical studies have been performed to confirm if LDE225 is a sensitive CYP3A4 substrate, *hence concomitant use of strong CYP3A4 inhibitors and inducers is not permitted*.

Patients receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. A partial list of drugs that are inducers, and inhibitors of CYP3A4/5 is included in the Table below. This list of medications has been generated by Novartis Oncology Clinical Pharmacology (OncCP) (DDI database document: last update August 2010) that is compiled by using information listed under “draft guidance for industry, drug interaction studies, CDER 2006”, Indiana University School of Medicine drug interaction tables at

http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable, and "drug interaction from University of Washington. Patients should be instructed *not to take grapefruit, St John Wort or Seville (sour) orange juice* while receiving LDE225 treatment throughout the study due to potential CYP3A4/5 inhibition. The other drugs without an asterisk should be carefully used as concomitant therapy.

Table Medications that are CYP3A4/5 inducers or inhibitors

Medications	
Inhibitors	**HIV antivirals:** indinavir, nelfinavir, ritonavir*, saquinavir **Antibiotics:** azithromycin, ciprofloxacin, chloramphenicol, clarithromycin, erythromycin*, fluconazole&, itraconazole*, ketoconazole*, voriconazole*, telithromycine, posaconazole, norfloxacin **Calcium channel blockers:** diltiazem&, verapamil& **Antidepressants:** , fluvoxamine, nefazodone* **Miscellaneous:** amiodarone, cimetidine, delavirdine, diethyl-dithiocarbamate (chlorzoxazone), interleukin-10*, mifepristone, mibefradil , grape fruit juice&, isoniazid&, apepritant&
Inducers	**HIV antivirals:** efavirenz, nevirapine **Anticonvulsants:** barbiturates**, carbamazepine**, oxcarbazepine**, phenytoin**, phenobarbital** **Systemic glucocorticoids:** dexamethasone&, glucocorticoids, hydrocortisone, prednisolone, prednisone **Antibiotics:** rifabutin**, rifampicin**,rifapentine** **Antidiabetics:** pioglitazone, troglitazone **Miscellaneous:** modafinil, hormone replacement therapy, oral contraceptives, St John's wort**

***- Known strong inhibitors of CYP3A4 are estimated to cause a ≥5 fold increase in the AUC values or a ≥80% decrease in clearance of a CYP3A4 substrate;**

& - a moderate inhibitor is estimated to cause a 2-5–fold increase in the AUC values or a 50-80% decrease in the clearance of a sensitive substrate when the inhibitor is given at the highest dose.

**** - Known strong inducers of CYP3A4/5 (AUC decrease by 50-80%)**

5.1.7.3 CYP2B6 and CYP2C9 substrates (narrow therapeutic index)

LDE225 is a potent inhibitor of drugs metabolized by the cytochromes CYP2B6 and CYP2C9 *in vitro*. Because of the potential risk for drug-drug interactions, using concomitant medications known to be metabolized by these enzymes that have low therapeutic index (see Table below) is not permitted in the study. The other drugs without an asterisk should be carefully used as concomitant therapy.

Table Drugs metabolized by CYP2B6 and CYP2C9

CYPs	***Drugs metabolized by CYPs***
CYP2B6	Bupropion , cyclophosphamide, efavirenz, ifosfamide, methadone
CYP2C9	**NSAIDs:** diclofenac, ibuprofen, lornoxicam, meloxicam, naproxen, piroxicam, suprofen **Oral hypoglycemic agents:** tolbutamide, glipizide **Angiotensin II blockers:** losartan, irbesartan **Sulfonylureas:** glyburide/glibenclamide, glipizide, glimepiride, tolbutamide

Miscellaneous: amitriptyline, celecoxib, fluoxetine, pravastatin[&], glyburide, nateglinide, phenytoin, rosiglitazone, tamoxifen, torsemide, warfarin*, quinidine*

* - narrow therapeutic index: drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsade de Pointes) are not allowed

[&] - **statins** – If it is essential that the patient takes a statin to control hyperlididemia [see Section 5.1.7.5], then only **pravastatin** may be used with extra caution. Pravastatin has the lowest potential of cause rhabdomyolysis compared with other statins (3 cases/ 6 millions of prescription from 1994 to 2002) (Evans et al. 2002) and the lowest risk for drug-drug interactions with LDE225, as it is primarily transformed in the liver cytosol by sulfonation, not by CYP2C9 or CYP3A4. (Evans et al. 2002)

5.1.7.4 Warfarin and coumadin derivatives

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-derivative anticoagulants are not permitted since LDE225 is a competitive inhibitor of CYP2C9 based on the *in vitro* data. An alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

5.1.7.5 Drugs that may increase risk of rhabdomyolysis

Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with LDE225 should be avoided. Such drugs should be discontinued for at least 2 weeks prior to initiation of LDE225 and it must be ensured the plasma CK is within the normal range at baseline. The list compiled below is based on reported association of the individual drugs with muscle toxicity and in addition to the potential risk of clinically relevant PK drug-drug interaction with LDE225 through inhibitory effects on CYP3A4 (enzyme metabolized LDE225) or the inhibitory effect on CYP2C9 by LDE225 of drugs that may induced rhabdomyolysis.

- Azoles: Itraconazole, ketoconazole, fluconazole, voriconazole
- Macrolides: Azithromycin, clarithromycin, erythromycin, telitromycin
- Fibrates: Gemfibrozil, fenofibrate
- HMG CoA reductase inhibitors* ("statins"): Atovastatin, Fluvastatin, Fluvastatin, Lovastatin, Rosuvastatin and Simvastatin
- Antiretrovirals: Indonavir and ritonavir
- Others: phenobarbital, barbiturates, phenytoin and isoniazid

** If it is essential that the patient stays on a statin to control hyperlididemia [see Section 5.1.7.5], only pravastatin may be used with extra caution; CK should be monitored weekly during treatment with LDE225.*

5.2 Study drug (LDE225)

5.2.1 Packaging and labeling

LDE225 capsules will be supplied by Novartis as 200-mg hard gelatin capsules for oral use, packaged in bottles, and will be administered on a flat scale of 800 mg/day for all patients.

Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number but no information about the patient.

Table Packaging and labeling

Study drugs	Packaging	Labeling (and dosing frequency)
LDE225	Capsules in bottles (200 mg)	Labeled as ”LDE225”

5.2.2 Supply, receipt and storage

Study drug must be received by a designated person at the study site (usually the site pharmacist), handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, LDE225 should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator’s site (usually the pharmacist).

Patients will be provided with adequate supply of LDE225 for self-administration at home until at least their next scheduled study visit (*i.e.* at least a 4-week period). Patients should be instructed to store LDE225 capsules in the refrigerator.

5.2.3 Drug compliance and accountability

5.2.3.1 Drug accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

5.2.4 Disposal and destruction

The drug supply will be destroyed at a Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the Investigational Site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

6 Schedule and Assessments

6.1 Study flow and visit schedule

	Screening Evaluation	Repeat Biopsy [a]	Day 1	Day 14	Prostatectomy, Day 28 (±3)	Follow-up, 1 mo Post-Op	Follow-up, 2 mo Post-Op	Follow-up, 3 mo Post-Op [j]
Informed consent	X							
Medical history	X			X	X			
Medication review	X			X	X			
Physical exam	X			X	X			X
Vital signs	X			X	X			X
Height and weight	X			X	X			
Performance status	X			X	X			X
ECG	X			X	X			
CT and bone scan [b]	X							
Heme labs, Coags [c]	X			X	X			X
Chemistries, incl. CK [d]	X			X	X			X
PSA (standard) [e]	X				X			X
PSA (ultrasensitive) [e]						X	X	
Plasma for PKs [f]	X				X			
LDE225 dose [g] (Arm 1)			X----------		----------X			
Observation [g] (Arm 2)			X----------		----------X			
Toxicity assessment			X----------		----------			----------X
Prostatectomy specimen [h]					X			
Pathologic review [i]	X	X			X			

a: A repeat 12-core (pre-treatment) prostate biopsy should be conducted within 4 weeks (±4 days) of starting protocol therapy. Tissue will be subject to mRNA analysis.

b: Staging CT (if allergic to CT scan contrast, obtain MRI with contrast); CT and Bone scan must be performed within 2 months of starting protocol therapy

c: Hematology laboratories include hemoglobin, hematocrit, white blood cell count with differential, and platelets. In addition, PT/INR and APTT should be collected.

d: Chemistry laboratories include sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, calcium, albumin, total protein, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase. In addition, creatine kinase (CK) should be measured at baseline, and then only for patients receiving LDE225.. Samples drawn for CK levels will be taken from both arms.

e: Serum PSA should be obtained pre-treatment and on the day of surgery, and at 1, 2 and 3 months post operatively. Ultrasensitive PSA testing should be run at the 1 and 2 month post-op time points.

f: Blood samples will be collected at baseline and on the day of prostatectomy for measurement of plasma LDE225 levels.

g: LDE225 800 mg by mouth once daily (for 4 weeks, ±3 days) OR observation. Patients randomized to the observation arm are not required to have the C1D14 visit.

h: Radical prostatectomy specimens to be processed at Johns Hopkins according to standard procedures, with additional 250-mg biopsies of prostate tissue frozen for analysis of mRNA expression and tissue LDE225 levels.

i: Pathological review of outside biopsy slides at the Johns Hopkins Hospital are required to confirm Gleason grade of disease at screening. Pathologic evaluation will also occur with frozen tissue from repeat biopsies and with tissue from radical prostatectomy.

j: The post-operative evaluation at 1 and 2 months after prostatectomy may take place over the telephone or in person, but patients are required to have labs collected as indicated above. The 3-month follow-up should involve an office visit. After the 3-month visit, PSA will continue to be collected according to the treating physician's standard practice (usually once every 3 months).

6.1.1 Screening Evaluation

The screening examination must start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The investigator must not start any study related procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.

6.2 Assessments

6.2.1 Efficacy assessments

The primary measures of efficacy in this trial are pharmacodynamic measured by the change in *Gli1* expression by qRT-PCR. In addition, efficacy will also be evaluated in secondary endpoints which will compare tumor stage, grade, surgical margin rates and tumor proliferation / apoptosis between treatment and observation arms. The proportion of patients with undetectable PSAs at three months will also be assessed in the two groups.

6.2.2 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), including serious adverse events, the monitoring of hematology, blood chemistry, ECG and the regular monitoring of vital signs, and physical condition as shown in corresponding tables. All patients will receive CK level monitoring at baseline, day 14 and day 28 with additional levels drawn in patients report symptoms of rhabdomyolysis during the study. For details on AE collection and reporting, refer to the Safety section in the protocol.

In addition, we will pay particular attention to peri-operative adverse events (intraoperative bleeding, increased operative time, increased hospital length of stay, increased postoperative infections, wound breakdowns, etc.). These will be monitored by review of in hospital records and post-operative clinic notes.

6.2.3 Pharmacokinetics

Plasma LDE225 trough levels (PK) will be measured at baseline and on the day of prostatectomy using LC-MS/MS.

6.2.4 Biomarkers

For analysis of *Gli1* expression, RNA will be purified using the RNeasy Minikit (Qiagen) and then cDNA will be synthesized according to standard procedures. Quantitative PCR will then be performed using the Taqman system with primers for *Gli1* and the reference gene *HPRT1*. Applied Biosystems software will be used to calculate threshold cycle values (and thus relative expression levels). Normalized changes in *Gli1* expression between each patient pre- and post-operatively and between each group (observation versus treatment arm) will be made with 2-sided pairwise comparisons considering $P < 0.05$ to be statistically significant.

Genome-wide mRNA expression data will also be collected with comparisons made both within and between treatment groups. This analysis will look for expression based indications of molecular pathway alterations upon exposure to LDE225 and will do so in an unbiased

way. For each array, data will be processed for statistical analysis using packages from R/Bioconductor with a mixed-effects model used to fit for each gene and to estimate expression differences between groups and an empirical Bayesian approach used to moderate log2 fold change standard errors. Functional themes will be obtained from Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, the Humna Protein Reference Databases and Molecular Signature Databases and used to perform enrichment analysis using Wilcoxon tests. Multiple testing corrections will be performed using the Benjamini-Hochberg method.

7 Safety Monitoring and Reporting

7.1 Adverse Events

7.1.1 Definitions and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

- if it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require therapy, and are recorded.

Information about all serious adverse events will be collected and recorded on the FDA MedWatch 3500a Form. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself an SAE, should also be reported on an SAE form or pregnancy form and be followed up to determine outcome, including spontaneous/voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any SAE occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

This is a DSMP Level II study under the SKCCC Data Safety Monitoring Plan (12/6/2012). Data Monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by the Principal Investigator and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

7.2 Instructions for rapid notification of serious adverse events

7.2.1 Reporting responsibility

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)

7.2.2 Reporting procedures

All SAEs are reported to the FDA by the trial's IND Sponsor-Investigator (Dr. Antonarakis) via the IND annual report per 21 CFR 312.33. All SAEs deemed unexpected and related to the investigational product qualify for expedited reporting and must be submitted to the FDA by the IND Sponsor-Investigator per 21 CFR 312.32 as shown immediately below. The IND Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Sponsor-Investigator to be possibly related to the use of LDE225 within 7 calendar-days of first learning of the event. An unexpected adverse event deemed possibly related to the use of an investigational study drug is defined as any adverse drug experience of which the specificity or severity is not consistent with the current investigator brochure, the general investigational plan, or elsewhere in the current application, as amended. Such reports are to be telephoned or faxed to the FDA within 7 calendar-days of first learning of the event. The IND Sponsor-Investigator is required to notify the FDA in a written IND Safety Report, of any serious, unexpected adverse event considered by the Sponsor-Investigator to be possibly related to the use of LDE225 within 15 calendar-days of first learning of the event.

In addition to the above, the investigator must complete the FDA MedWatch 3500a form and Novartis SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Novartis SAE coversheet by fax 1.888.299.4565 within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis DS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Novartis

SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The MedWatch form, Novartis SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

7.3 Pregnancies

Each pregnancy occurring for a female partner of a male study participant must be reported while the patient is on study treatment and for up to 6 months after the patient's last dose. Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study.

8 Statistical Methods and Data Analysis

In general terms, we wish to determine if there is a statistically significant reduction in *Gli1* expression in prostate tissue after a 4-week exposure to LDE225. We expect to see significant down-regulation of *Gli1* in the treatment arm compared to the observational arm.

8.1 Sample size considerations, and analysis of the primary endpoint

The primary endpoint is a ≥50% reduction in *Gli1* mRNA (or protein) expression following treatment with LDE225. This study will compare prostatectomy *Gli1* expression levels to presurgical biopsy *Gli1* expression levels in the same patients (*i.e.* intra-patient changes). In the control group (observation), we expect <10% of patients to show a ≥50% *Gli1* downregulation (null hypothesis), while in the LDE225 group we would hypothesize that >50% of patients would demonstrate a ≥70% *Gli1* downregulation (alternative hypothesis). Using a 2-sided alpha (α) of 0.10 and a beta (β) of 0.20 (power = 80%), a sample size of **11 men/arm** (total = **22men**) would be required to observe a difference in the primary endpoint from <10% (in the control arm) to ≥70% (in the LDE225 arm).

8.2 Analysis of the secondary endpoints

- **Apoptotic markers.** Caspase 3 staining (and/or TUNEL assay results) will be expressed as the mean staining percentage in tumor samples, and reported separately for each treatment group. Standard deviations, 95% confidence intervals, and ranges will also be reported where appropriate. Means will be compared across treatment arms using two-way ANOVA.

- **Proliferation markers.** Ki-67 staining will be expressed as the mean staining percentage in tumor samples, reported separately for each treatment arm. Standard deviations, 95% confidence intervals, and ranges will also be reported where appropriate. Means will be compared across treatment arms using two-way ANOVA.

- **Pathological complete responses (pCR).** This will be defined as an absence of tumor identification on standard histological analysis of the resected prostate specimens. The proportion of patients achieving a pCR will be compared between treatment arms using the Mantel-Haenszel test.

- **PSA response rates.** This will be defined as an undetectable PSA (<0.1 ng/mL) at 3 months after prostatectomy. The proportion of patients achieving a PSA response will be compared between treatment arms using the Mantel-Haenszel test.

8.3 Analysis of the exploratory endpoints

Genome-wide mRNA expression data will also be collected with comparisons made both within and between treatment groups. This analysis will look for expression based indications of molecular pathway alterations upon exposure to LDE225 and will do so in an unbiased way. For each array, data will be processed for statistical analysis using packages from R/Bioconductor with a mixed-effects model used to fit for each gene and to estimate expression differences between groups and an empirical Bayesian approach used to moderate log2 fold change standard errors. Functional themes will be obtained from Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, the Humna Protein Reference Databases and Molecular Signature Databases and used to perform enrichment analysis using Wilcoxon tests. Multiple testing corrections will be performed using the Benjamini-Hochberg method.

9 Ethical Considerations

9.1 Ethics and good clinical practice

This study must be carried out in compliance with the protocol and GCP, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

9.2 Institutional review board / Independent ethics committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

9.3 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he may withdraw from the study at any time

and that withdrawal of consent will not affect his subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

Fertile men should be informed that taking the study medication may involve unknown risks to a conceived fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

9.4 Discontinuation of the study

Novartis reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

9.5 Amendments to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Novartis.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

9.5.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

9.5.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators'

brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

9.5.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

10 References

Aaronson NK, Ahmedzai S, Bergman B, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute; 85: 365-76.

Ahnert JR, Baselga J, Tawbi A et al (2010) A phase I dose-escalation study of LDE225, a smoothened (Smo) antagonist, in patients with advanced solid tumors. J Clinical Oncol 28:15s (Supple; abstr 2500)

Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. (199) Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. Journal of Clinical Oncology; 17: 1008-19.

Costantino D, Lowe L, Brown DL, et al (2006) Basosquamous carcinoma- an under-recognized, high-risk cutaneous neoplasm: case study of the literature. J Plast Reconstr Aesthet Surg; 59:424-8.

Daya-Grosjean L, Couve-Privat S (2005) Sonic hedgehog signaling in basal cell carcinomas. Cancer Letter; 225:181-192.

De Rie MA, Skvara H, Mickel L et al (2010) A double-blind, randomized, vehicle-controlled proof of concept study to evaluate the safety, local tolerability, pharmacokinetics and pharmacodynamics of multiple topical administrations of LDE225 (a specific Smoothened inhibitor) on skin basal cell carcinomas in Nevoid Basal Cell Carcinoma Syndrome (NBCCS) patients. Poster presentation at SID (05-08 May2010); 524 Abstract.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer;45: 228-247

Evans M, Rees A (2002) Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same.Drug Saf 25 (9):649-63

Fayers PM, Aaronson NK, Bjordal K et al. (2001) The EORTC QLQ-C30 Scoring Manual (3rd Edition). European Organisation for Research and Treatment of Cancer.

Flockhart DA. (2007). Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine, Version 5.0 released on January 12, 2009 (Internet) Available from: <http://medicine.iupui.edu/flockhart/table.htm> (Accessed 30 Nov 2010)

Food and Drug Administration (FDA) (2006). Guidance for Industry, Drug Interaction Studies - Study Design, Data Analysis and Implications for Dosing and Labeling, Center for Drug Evaluation and Research (CDER), Draft Guidance (Internet) Available from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm> (Accessed 30 Nov 2010

Gailani MR, StahleBackdahl M, Leffell DJ, et al (1996) The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas. Nature Genetics; 14: 78-81.

Johns D, Andersen JS (1999) Use of Predictive probabilities in Phase II and Phase III Clinical trials. Journal of Biopharmaceutical Statistics; 9:67-79

Kimura H, Ng JM, Curran T (2008) Transient Inhibition of the Hedgehog Pathway in Young Mice Causes Permanent Defects in Bone Structure. Cancer Cell;13:249-260.

Maeda Y, Nakamura E, Nguyen MT, et al. (2007) Indian Hedgehog produced by postnatal chondrocytes is essential for maintaining a growth plate and trabecular bone. The National Academy Sciences of the USA;104:6382-87.

Malone JO, Fedok FG, Belchis DA et al (2000) Basal Cell Carcinoma metastatic to the parotid: report of a new case and review of the literature. Ear Nose Throat J; 79: 511-5, 518-9.

Marcil I, Stern R (2000) Risk of Developing a Subsequent Nonmelanoma Skin Cancer in Patients with History of Nonmelanoma Skin Cancer. Arch Dermatol;136:1524-30.

Muzio L L (2008) Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet Journal of Rare Diseases; 3:32-48.

Mosterd K, Arits A, Thissen M et al (2009) Histology-based treatment of basal cell carcinoma. ACTA Derm Venereol; 89:454-58

Rubin AI, Chen EH, Ratner D (2005) Current Concepts: Basal-Cell Carcinoma. N Engl J Med; 353:2262-9.

Rogers HW, Weinstock MA, Harris AR et al (2010) Incidence Estimate of Nonmelanoma Skin Cancer in the United States, 2006. Arch Dermatol; 146:283-7.

Scales SJ, De Sauvage FJ (2009) Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. Trends in Pharmacolgical Sciences;30:303-12.

Telfer NR, Colver GB, Morton CA (2008). Guidelines for the management of basal cell carcinoma. Br J Dermatol ;159(1):35-48.

University of Washington, Department of Pharmaceutics (2008). Metabolism and Transport Drug Interaction Database, Version 4.0 (Internet) Available from: <http://www.druginteractioninfo.org> (Accessed 30 Nov 2010)

US Department of Health and Human Services (2007) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. FDA

Vantuchova Y, Curik R (2006). Histological types of basal cell carcinoma. Scripta Medica (BRNO); 78:261-70

Von Hoff DD, LoRusso P M, Rudin C M, et al (2009) Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma. N Engl J Med; 361:1-9.

Wong C S M, Strange R C, Lear J T (2003) Basal Cell Carcinoma. BMJ; 327:794-798.