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PSCI-21-173 Angelica Herbal Supplement AGN-CogniQ Acute Dose Safety and Pharmacokinetics (PK) Dose-Response in Prostate Cancer Patients (PK Dose Trial)

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1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

The long-term goal of our research is to conduct human clinical trials to test *Angelica gigas* Nakai (AGN) root alcoholic extract herbal supplement product (AGN-CognI.Q, or CognI.Q™, made with INM®176 proprietary ingredient, Quality of Life Laboratories, Purchase, NY) as a safe and potential efficacious modality for prostate cancer interception akin to secondary prevention to delay hormonal therapy or avoid it entirely after patients have developed recurrent disease following their standard of care (SOC) surgery and radiation curative treatment.

The specific objectives of the current IRB protocol are to obtain acute dose safety and pharmacokinetics PK (the study of how our body handles a given drug) and pharmacodynamics PD (the study of what the drug does to our body) data in a single ascending dose (SAD)-PK response trial in prostate cancer patients. We hypothesize that AGN-CognI.Q at the high doses is safe and has an acceptable toxicity profile in prostate cancer patients and PK exposure metrics will be increased proportional to dose increment. We anticipate that the acute dose safety and PK/PD information from the current proposed acute PK dose-response trial will inform the optimal design and execution of the longer-term safety and efficacy (phase I/II) trials.

1.1.1 The primary objective is to estimate the maximum tolerated dose of AGN-CognI.Q. Subjects (total sample size n = 12 evaluable subjects), each for 4 ascending AGN-CognI.Q dose levels in the form of AGN-CognI.Q capsules (up to 10 capsules per dose), for single-dose safety metrics with a 1-week washout between doses.

1.1.2 The secondary objectives are several fold:

1.1.2.1 To determine dose-response of PK metrics (especially uptake and exposure) for AGN pyranocoumarin compounds to AGN-CognI.Q supplement. The data will inform whether a metabolism capacity ceiling exists for parent compounds decursin and decursinol angelate (D, DA) and their metabolite decursinol (DOH).

1.1.2.2 To genotype CYP 2C19 and 3A4 metabolizer status and explore relationship to PK metrics and safety metrics.

1.1.2.3 To explore responses of immunology tests as PD biomarkers.

1.1.2.4 To evaluate changes in body temperature during each course of PK blood collection as another potential PD response biomarker.

1.1.2.5 To evaluate clinical safety/toxicity according to NCI Common Terminology Criteria for Adverse Events (CTCAE version 5.0) as standard of care.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

Acute safety is assessed by the integration of three types of metrics below

1. Monitor cardiac safety with electrocardiography (EKG) (12-leads EKG) at baseline, and at 5 hours.
2. Monitor safety blood lab tests at 24 h and before the next dose level.

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

1. To determine the PK metrics of decursin (D) and its isomer decursinol angelate (DA) and their metabolite decursinol (DOH) after each AGN-CognI.Q dose of the single dose escalation series. Blood will be collected at pre-each dose baseline (**0 h labs= baseline**), **2h 3h 4h 5h 6h, 7 h** and **24 h** (frequency guided by Zhang et al, PLOS 1, 2015[1] and patient comfort and protocol compliance) to estimate *peak concentration* C_{max}, and *area under curve AUC*). The $AUC_{0\text{-}24h}$ and C_{max}-dose curves for D, DA and DOH for each subject will be evaluated for dose proportionality to inform any metabolic ceiling for dose-escalation in Phase I trial (Under a separate IRB protocol).
2. To genotype Cyp 2C19 and 3A4 isoforms and associate with PK exposure metrics (C_{max}, $AUC_{0\text{-}24h}$) and safety outcomes.
3. To measure changes in immune cell phenotypes (the number and or activation state of NK and other immune cells by flow cytometric quantitation) from base line to 24 h (+/-2 h) (day 2) after administration of each AGN-CognI.Q dose. Blood samples will be taken at baseline and on day 2 of each dose per subject.
4. To record body temperature before each dose (baseline) and during each course of blood collection.
5. To evaluate clinical safety/toxicity according to CTCAE version 5.0, from first dose of the study drug to 4 weeks (± 7 calendar days) following last dose.

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the treatment, drug, or device is available to patient without taking part in the study.

Early stage operable intermediate and high-risk prostate cancer (PCa) is treated with a curative intent with radical prostatectomy (RP) and radiation therapy (RT) as standard of care (SOC). However, a significant proportion of the treated patients will develop recurrent disease and some of them will be treated by hormonal therapy commonly known as androgen deprivation therapy (ADT; i.e., medical or surgical castration) as the SOC option. ADT, however, is not curative and causes many serious adverse effects, including sexual dysfunction/impotence, osteoporosis and bone fractures, wild mode swings, hot flashes, fatigue, loss of lean body mass, gynecomastia and anemia. There is currently no FDA-approved treatment for patients in the clinical space post-RP and RT and prior to ADT. There is a clear and significant unmet clinical need in this patient population to control and intercept their disease progression and maintain their quality of life.

The goal of our research is to test *Angelica gigas* Nakai (AGN) root alcoholic extract herbal supplement as a safe and potential efficacious modality for PCa interception akin to secondary prevention to delay ADT or avoid it entirely. With mechanisms distinct from currently approved ADT, next-gen androgen and its receptor targeted- or SOC chemotherapy drugs, we **hypothesize** that (**1**) the PCa interception bioactivity by AGN and its pyranocoumarins in animal cancer models is extendable into human PCa patients, given sufficient AGN dosage and exposure duration; and (**2**) multiple mechanisms, including immune surveillance and suppression of inflammation, contribute to the cancer inhibition. The **scientific premise** is based on the presence of novel active pyranocoumarin compounds (**Fig. 1**) *distinct* from those in soy, tea, fish oil, raspberries, mushrooms, and cannabis

and reported broad-spectrum anti-cancer efficacy in various animal models. Moreover, we have demonstrated a) Oral bioavailability and favorable pharmacokinetic (PK) metrics in rodents and in humans (NCT02114957) [1](Seep previous data section); b) Cytochrome P450 (CYP) 2C19 and 3A4 first-pass conversion of pyranocoumarins decursin (D) and decursinol angelate (DA) to the *in vivo* active metabolite decursinol (DOH)[2]; c) Proficient tissue retention of decursinol in mouse target prostate[3]; d) Animal modeling of AGN and decursinol showing independence of the androgen receptor (AR) axis, avoiding side effects of ADT drugs and making blood levels of prostate specific antigen (PSA) a reliable readout for PCa burden (See data section); e) AGN enhanced immune and decreased inflammatory gene signatures in an animal PCa model[4]; and f) A single AGN dose in human subjects increased natural killer (NK) mRNA signature and decreased IL-8 chemokine mRNA in their peripheral blood mononuclear cells (PBMC) (See data section); and g) pain killing in rodent models with decursinol led to hypothermia (See data section).

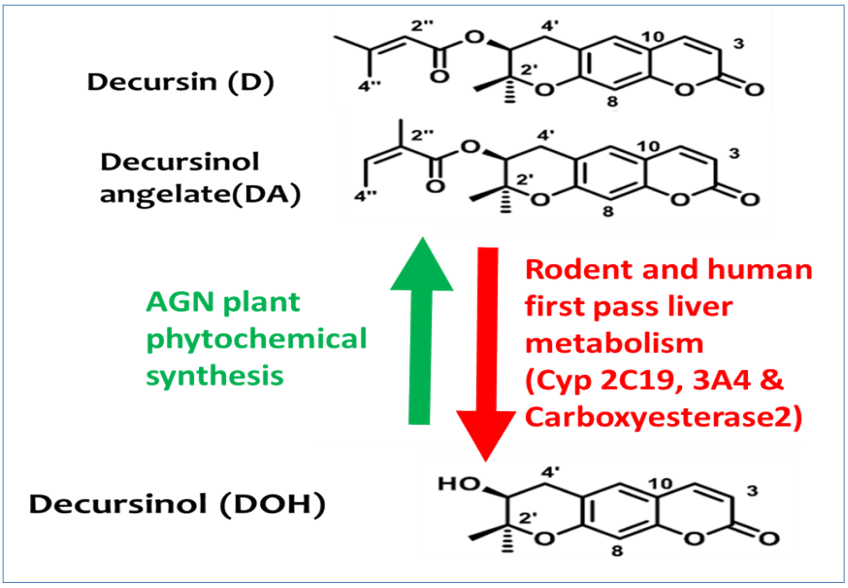


Fig 1. Chemical structure of signature pyranocoumarins in AGN root and their interrelationship in botanical synthesis (green) and metabolism in rodents and humans (red). CES2 – Carboxyesterase-2. Cyp – Cytochrome P450.

We propose to carry out a number of early stage human intervention trials in post-RP and post-RT patients with rising plasma PSA that is "clean" (i.e., prostate with primary PCa already removed) and highly indicative of the biochemically recurrent PCa burden to obtain efficacy signals under the best achievable test condition (i.e., optimized dosing regimen, sufficient dosage and minimal adverse effect.

The PK dose-response trial (current IRB protocol, addressing NCI Grant Aim 1) and the planned Phase I/II early stage clinical trials (NCI grant Aim 2, under a Separate IRB protocol) take advantage of a niche prostate cancer patient cohort who have failed local "curative" therapies to address a significant unmet clinical need in a sizable recurrent cancer patient population who would otherwise soon face current SOC hormonal therapy known as androgen deprivation therapy (ADT) through medical or surgical castration. Not only expensive, ADT also causes many serious and unpleasant side effects including sexual dysfunction/impotence, osteoporosis and bone fractures, wild mode swings, hot flashes, fatigue, loss of lean body mass, gynecomastia and anemia. In spite of multiple next-gen androgen and its receptor targeted drugs (e.g., abiraterone acetate, enzalutamide), DNA-repair drugs (PARP inhibitors) and microtubule targeting taxane drugs indicated for managing even more advanced stage diseases, there is currently no FDA-approved modality before ADT to intercept or delay disease progression for this patient population. There is a clear need for modalities that are safer, efficacious and less objectionable in terms of quality of life of patients. Why test *Angelica gigas* Nakai (AGN) herbal supplement?

The dried roots of *Angelica gigas* Nakai (AGN, also known as Korean Angelica, Giant Angelica, Korean Dang Gui) and its Chinese counterpart, *A. sinensis* (Dang Gui*),* have been used in traditional herbal medicine for centuries [5, 6]. AGN differs from other medicinal Angelica species including *A. sinensis* and *A. acutiloba* (Japanese) by its possession of decursin (D) and its structural isomer decursinol angelate (DA), plus trace amount of decursinol (DOH) [6] (**Fig. 1**). Regarded by herbalists as "female Ginseng" for its blood and health promoting activities, AGN has been used for the treatment of menstrual blood loss, physical weakness, joint pain, abdominal pain and constipation [6]. However, these traditional uses were mostly based on using boiling water to extract the active ingredients. Changing the extraction solvents can lead to the recovery of different phytochemicals and novel pharmacological properties. Many pyranocoumarins have been identified from alcoholic extract of AGN [7, 8] which could not be extracted by water [9].

Herbal dietary supplement products containing/based on AGN alcoholic extracts (including CognI.Q; Decursinol-50™, GWB78®, Ache Action, Fast-Acting Joint Formula, EstroG-100/Profemin) are marketed in the US for memory enhancement, pain relief and for women's post-menopausal symptom management [6, 10]. Daily intake recommended for these conditions ranges from 500 mg to 800 mg AGN extract in the form of INM-176, a patented ethanolic extract powder, as the active ingredient used in the above products.

In terms of PCa interception or prevention, **human efficacy testing for AGN-CognI.Q supplement in cancer patients is supported by strong scientific premise.** The pyranocoumarins belong to a new class of "active" phytochemicals *distinct* from those in other dietary/herbal "remedies" or their combinations, including soy, tea, fish oil, berries, mushrooms, or cannabis, etc. Their chemical structure uniqueness offers research opportunity to complement and synergize with other remedies.

The premise was further evident from the other reported *in vivo* bioactivities of AGN alcoholic extracts (AGN AE) and tested pyranocoumarins (D, DA or their metabolite decursinol) (see **summary chart in Figure 2**). In addition to our PCa work, AGN AE, D/DA or DOH have been reported to suppress the *in vivo* growth and/or metastasis of sarcoma [14], lung cancer [8 15] and colon cancer metastasis to lung [16] and melanoma[17].

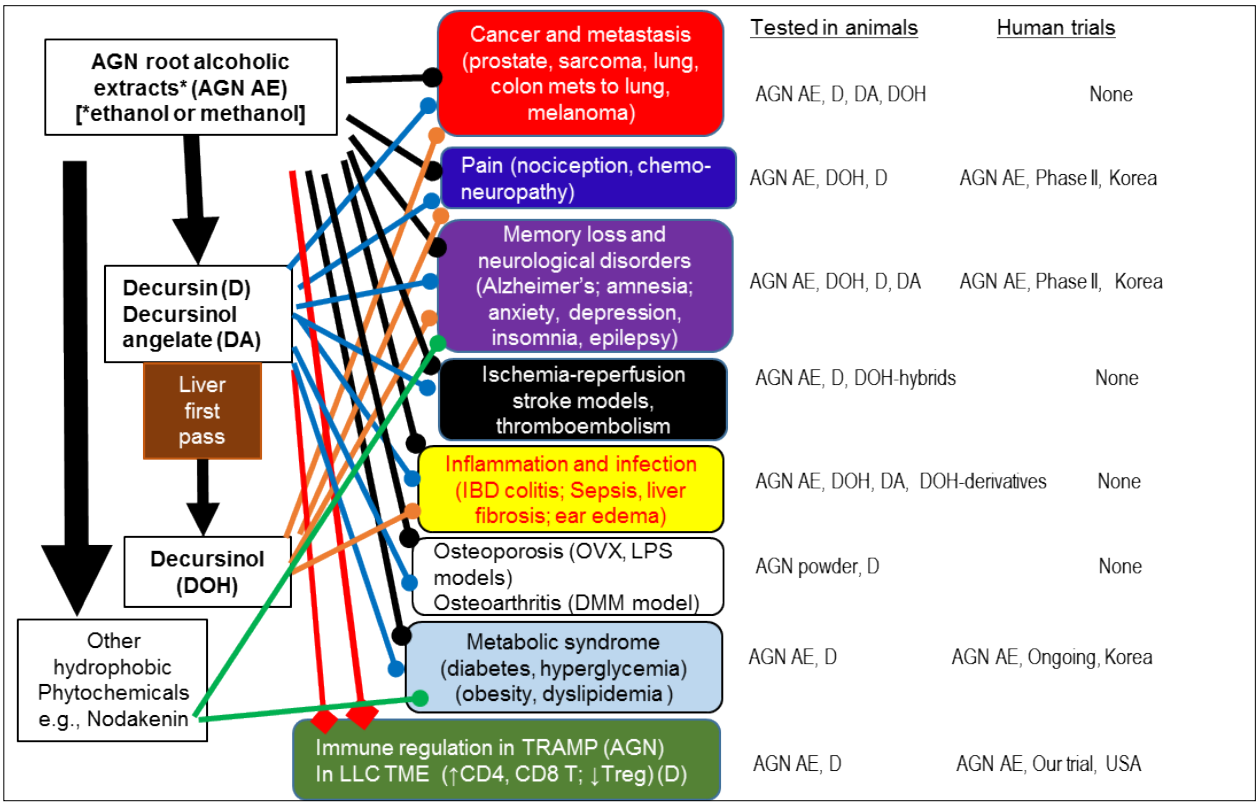


Fig. 2 Reported bioactivities of AGN alcoholic extracts, their pyranocoumarins and other hydrophobic compounds in preclinical animal models and human clinical trial status.

In reference to tumor immune regulation as potential PD biomarkers, it was reported in 2020 that *in vivo* decursin treatment increased CD4 and CD8 T cells and decreased inhibitory T_{regs} in the TME of mouse LLC lung cancer syngeneic model [15]. The water extract (AGN WE) termed angelan, composed of pectic polysaccharides, exhibited immune stimulatory activities *in vitro* and in animal models [18] [19-22]. A similar water extract named ISAg (immune-stimulatory component of AGN) has been shown to activate NK and NKT cells against B16 melanoma in syngeneic mice [23, 24].

Moreover, two cases of elderly Korean cancer patients with multiple comorbidities were reported [25], documenting remarkable cancer responses from taking AGN with 10 other herbals and vast improvement of their health status. In the 73-year old man with lymphoma, gastric cancer and metastatic PCa, his PSA decreased from 286.1 ng/ml at start of herbal medicine to 0.046 ng/ml after 4 months [25]. Even though the efficacy cannot be attributed to AGN alone, the cancer patients' herbal medicine exposure experience is noteworthy.

Knowledge gap: So far only one dose of AGN-CognI.Q (**current dietary supplement dose**) has been studied in humans for the PK metrics [1] (see Previous data). Based on animal cancer model studies, we anticipate that higher dose exposure is necessary to achieve cancer interception. However, the safety of higher doses and the dose-response nature of PK metrics to increased AGN-CognI.Q dosages in humans, especially in older cancer patients, have never been reported and remain an important knowledge gap. The feasibility for swallowing up to 10 capsules, twice a day for the proposed Phase I/II trial (Aim 2 of NCI grant) has not been tested in our patient cohort.

In addition, whether AGN-CognI.Q should be taken on empty stomach or can be taken with food and if so, whether high fat vs. low fat food to minimize negative interaction of pyranocoumarin uptake and exposure are important dosing regimen optimization questions. Such practical information supports FDA-required drug label.

Furthermore, our preclinical animal studies and earlier human study have suggested immune enhancement and suppression of inflammation (See Previous data section below) as potential PD biomarkers of AGN intake. The acute effects of increasing dosages of AGN-CognI.Q on these metrics will be explored to inform and support selection of PD biomarkers in the Phase I/II trials.

Moreover, in rodent experiments for pain relief studies, we have observed decursinol-induced hypothermia (lowering of body temperature) in direct proportion to the extent of pain killing (See Previous data section below). Therefore, we propose to explore body temperature response as another potential PD biomarker metric.

An exactly defined patient population is potentially less important in a PK study than in Phase I-III trials, therefore, once the maximal tolerated dose (MTD) is established in a similar but not an exact patient population in the current PK dose-response study, we will be testing the drug in a patient population of post-RP or post RT with biochemically recurrent prostate cancer. We do not anticipate that the adverse events (AEs) will change in the above patient population. However, while doing the follow up study, we will be monitoring for AEs in that group as well.

Therefore, the PK dose-response trial will generate the practical knowledge/evidence for guiding safety monitoring, dose-escalation range and dosing regimen for the Phase I/II trials (NCI grant Aim 2) and will inform and streamline the selection of PD biomarkers. Together, these early stage trials will provide the first of its kind knowledge of safety and preliminary efficacy of an AGN-CognI.Q herbal supplement against prostate cancer at therapeutic dosages, with mechanisms of action distinct from the currently approved drugs and more favorable safety profiles. The novel dose-exposure PK/PD information from these trials will be applicable to other patient populations to evaluate prevention and therapy of other cancers as well as other diseases.

2.2 Previous Data

Describe any relevant preliminary data.

2.2.1 PK and metabolism in human

2.2.1.1 PK study In terms of how humans process AGN herbal supplement after oral intake, we completed the **first-in-human PK study** of its signature pyranocoumarin compounds after a single dose of AGN (commercial

product AGN-CognI.Q) (800 mg) [1] (**Fig. 3**), With T_{max} = 3.3 h, the single dose C_{max} of 2.2 µM decursinol in human (**Fig. 3**) is within achievable range of the rat C_{max} values (5-7 µM with ~5 x allometric D/DA dosed per rat [26] and mouse values (e.g., 60 µM with ~9 x allometric D/DA dosed per mouse [3, 27]).

2.2.1.2 In vitro and in vivo metabolism We have shown hepatic cytochrome P450 (CYP) 2C19 and 3A4 isoforms are crucial for D and DA conversion to decursinol [2]. The human PK study outcome and enzyme essays in vitro confirmed the extensive first pass conversion of D/DA in liver to decursinol in both humans and in rodent models [2, 10, 26, 27] **Fig. 4 shows the most up to date metabolism chart of ingested pyranocoumarins.**

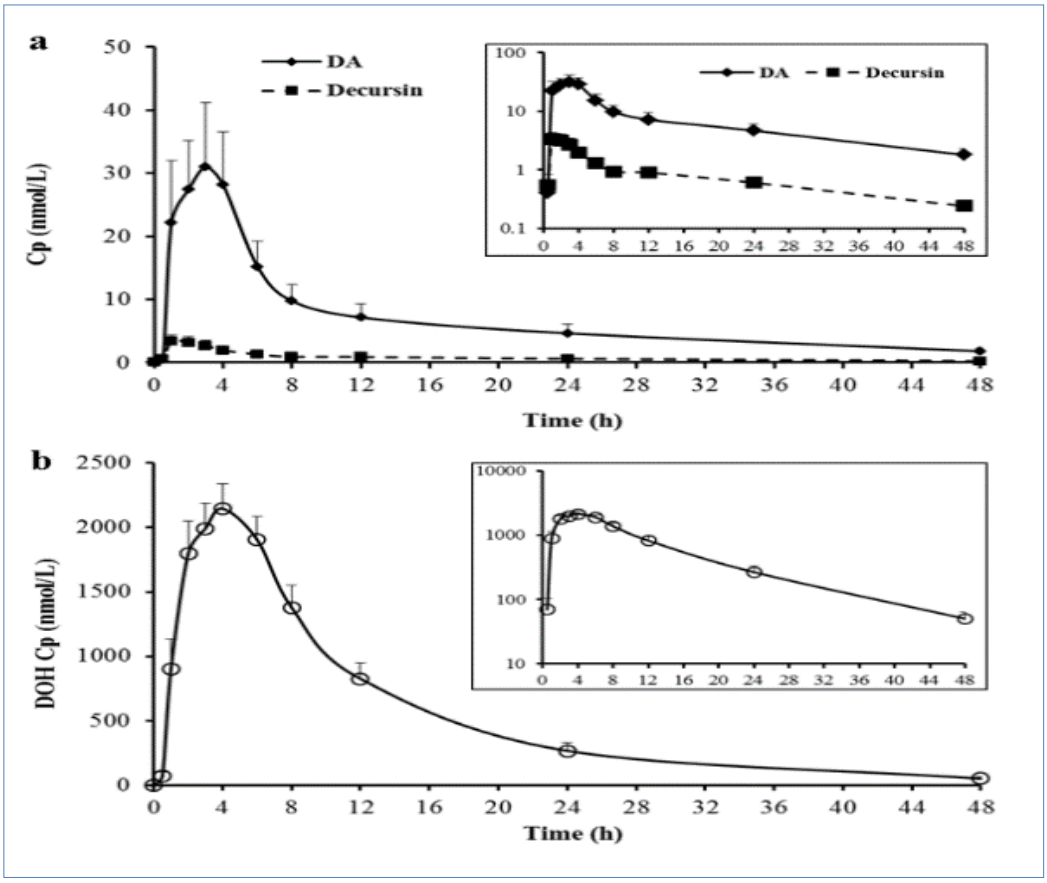


Fig. 3 First-in-human PK data. Human plasma (**a**) D, DA & (**b**) DOH concentration (nM) vs. time. Insets are data presented on semi-log scale. Mean + sem, n=20. Each person took 4 AGN-CognI.Q capsules (800 mg INM-176 AGN) at time 0.

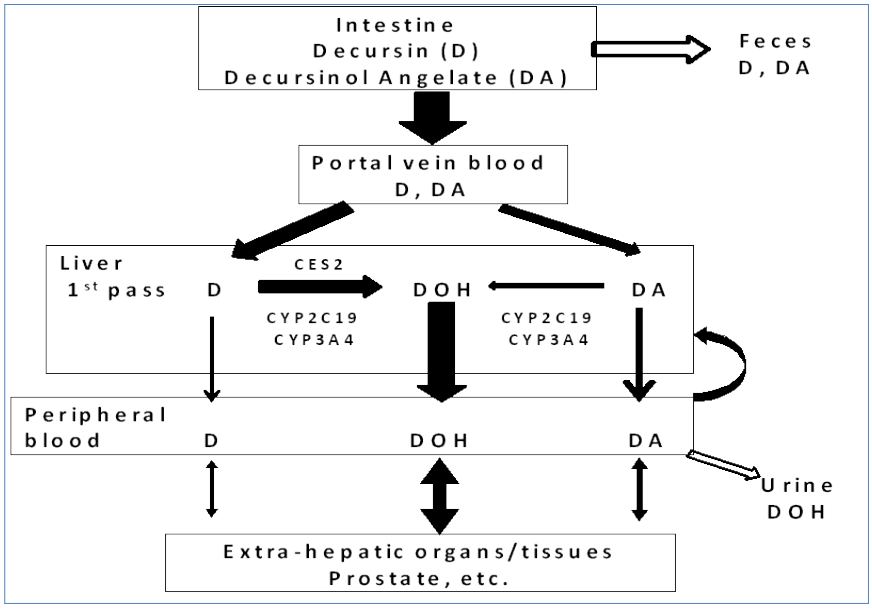


Fig 4. Current knowledge of metabolism of ingested pyranocoumarins in rodents and humans. CES2 – Carboxyesterase-2. CYP – Cytochrome P450.

2.2.2 Potential immunology and inflammation PD biomarkers

Natural killer (NK) cells search out and kill cancer cells and virus-infected cells that have dysregulation of cell surface markers [28] [29]. This is mediated by granzyme serine-proteases released from cytoplasmic granules that enter target cells [30] through a multimeric complex made up of granzyme B, perforin, and granulysin to trigger apoptosis through caspases. NK cells secrete interferon gamma (IFNγ) that stimulates neutrophil gene expression, including chemokine receptors, and activates phagocytic functions.

In our single dose PK study [1] (Fig. 3), RNA was isolated from PBMC from pre-dose baseline blood and 24 h after AGN-CognI.Q using QIAamp® RNA Blood Mini kit (QIAGEN). The mRNA expression from 6 subjects was profiled using the Illumina Human HT-12 BeadChip array. All RNA labeling and hybridization were performed as before [4]. **NK-signature genes** were prominently affected compared to baseline (**Table 1**)**.**

Table 1. Enriched pathways 24h post-AGN-CognI.Q vs. baseline in PBMC mRNA by microarray profiling

Pathway name	Pathway source	# genes	Overlapping genes	P values
Natural killer cell mediated cytotoxicity - (human)	KEGG	5	*KLRD1;GZMB;KIR2DL3;KIR2DL4;PRF1*	1.06E-05
Graft-versus-host disease -(human)	KEGG	4	*KLRD1;GZMB;KIR2DL3;PRF1*	1.95E-06
IL12-mediated signaling events (NK)	PID	4	*EOMES;CCL4L2;GZMB;GZMA*	1.18E-05
Immuno-interactions between Lymphoid and non-Lymphoid cell	Reactome	4	*KLRD1;KIR2DL3;KIR2DL4;CD160*	0.000119
Granzyme a mediated apoptosis pathway (NK)	BioCarta	3	*GZMA;GZMB;PRF1*	1.67E-06

Real-time RT-PCR quantitation was carried out as before[4] to verify select genes, normalized to housekeeping gene *β-actin* (**Fig. 5A)**. The levels of PBMC NK mRNA markers were ~60-90% higher for 24 h post-dose vs. baseline (n = 6, p<0.01) (**Fig. 5A**). The increased anti-inflammatory prostaglandin D axis genes and GPR56 in PBMC, 24 h post- AGN-CognI.Q, are noteworthy. PTGDS is found to be lower in PCa vs. prostate tissue [31]. The

PTGDS/PTGDR axis suppresses intestinal carcinogenesis in Apc$^{min/+}$ mice [32] and gastric cancer stem cells [33]. GPR56 acts as prostate specific tumor suppressor against mouse TRAMP tumors [34].

However, not all genes changed in the same direction (i.e., unlikely systematically biased). The inflammatory cytokine *IL-8* mRNA decreased post dose (Fig. 5A).

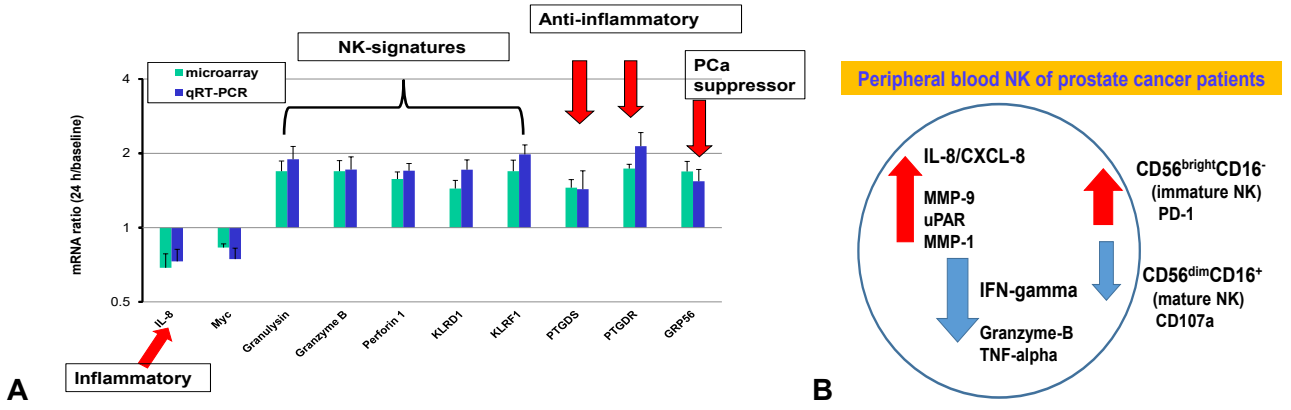


Fig. 5A Select PBMC mRNA changes from pre-dose baseline detected by microarray and qRT-PCR suggest NK and anti-inflammation signatures of AGN-CognI.Q. N = 6 subjects. **5B**. Latest view of NK cell characteristics from prostate cancer patients.

<u>IL-8 axis and NK in PCa as relevant "targets" for AGN-CognI.Q.</u> Prostate cancer overexpresses IL-8 [35, 36 37-39] known to drive inflammation, neo-angiogenesis and metastasis [40]. A US-led study showed higher baseline serum IL-8 at start of ADT portended worse survival and shorter time to castration-resistant PCa independent of docetaxel administration and metastatic burden [41], in contrast to an earlier study from Belgium that showed no correlation [42]. Integrative transcriptomic analyses of more than 9000 prostatectomy microarrays for PCa immune landscape showed that enrichment of NK gene signatures associated with improved distant metastasis free survival of the locally-treated patients [43]. A machine learning approach based on peripheral blood NK (pNK) subset phenotyping data showed a utility to identify PCa and its clinical risk in asymptomatic men [44].

NK cells search and kill malignant cells [28], but human NK activation is hampered by the immunosuppressive prostate tumor microenvironment (TME), as shown by French scientists [37]. They examined the frequency, phenotype, and functions of NK cells infiltrating the "normal" prostate tissue and PCa. The NK infiltrates in prostate tissues were mainly CD56 (NCAM1)-positive and displayed an unexpected immature, but activated, phenotype with low or no cytotoxic potential. Furthermore, they showed that paracrine cytokine TGFbeta1 was highly secreted into the prostate environment and partly mediated the immunosuppressive effects on NK cells.

Their conclusion was extended by an Italian study reported in 2021 that peripheral NK (pNK) cells from PCa patients acquired the CD56(^{bright}, immature)CD9(+)CD49a(+)CXCR4(+) phenotype, increased the expression of markers of exhaustion (PD-1, TIM-3) and were impaired in their degranulation capabilities [45]. They also observed that healthy donor-derived pNK cells exposed to conditioned media of three different PCa cell lines experienced similar shift of maturation status plus increased production of pro-inflammatory chemokines/receptors **CXCL8** (**IL-8**), CXCL12 and CXCR4, reduced production of TNFα, **IFNγ** and granzyme-B (**Fig. 5B**). Their additional results show that PCa infiltrated/associated pNK acquired properties of pro-inflammatory angiogenesis in endothelial cells, recruited monocytes and polarized macrophage into an inflammatory M2-like phenotype [45].

The impaired NK function in PCa patients has been further supported by using a streamlined NK activity (NKA) assay initially developed by Korean scientists [46-48] using 1-ml whole blood in cytokine-preloaded NKVUE collection tube for 24 h ex vivo. The IFNγ released into sera samples will be quantified by ELISA as NKA. The NKVUE NKA has been applied to PCa patients in Korea [48], Canada [46], US [49] and Taiwan [50], documenting significant NKA deficit than in non-cancer controls, with added diagnostic and prognostic values.

2.2.3 Hypothermia effect of decursinol

In unpublished animal pain model studies (Daniel Morgan and Lu labs), a reduction of rectal temperature of the mice administered decursinol was observed (**Fig. 6A**) in close dose-dependent association with thermal pain killing efficacy assessed as tail flick response (**Fig. 6B**) and as hot plate paw withdrawal response (**Fig. 6C**). Therefore, body temperature of the patients will be taken before and after AGN-CognI.Q dosing as another easily assessable potential PD biomarker.

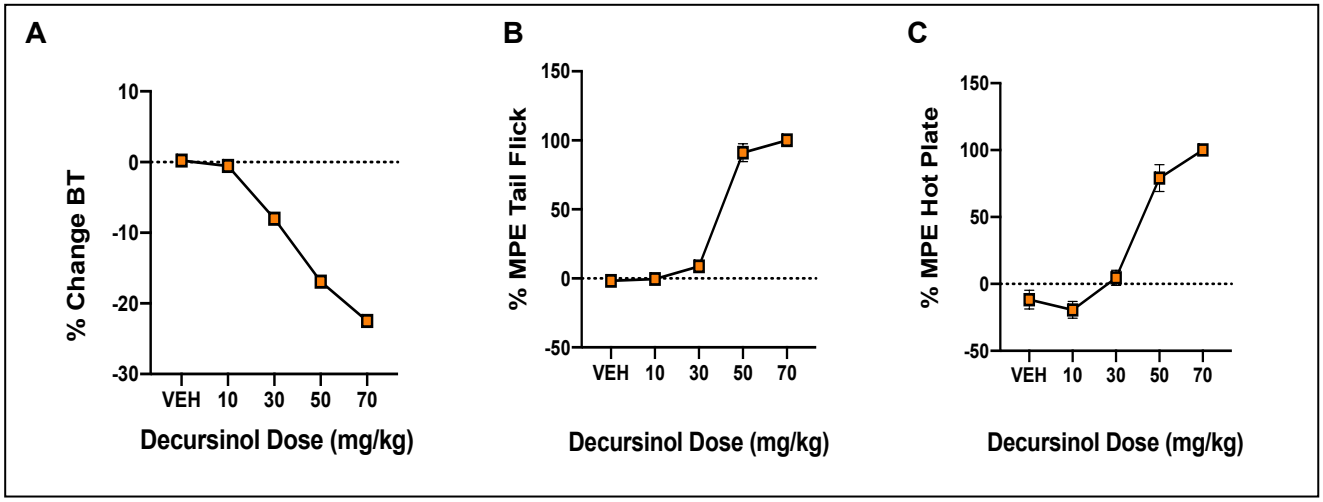


Fig.6 Hypothermia induction (A) and pain relief responses (B&C) in mice by decursinol (i.p.). **A.** Rectal temperature change from pre-dose baseline induced by increasing doses of decursinol, measured 30 minutes after each dosing regimen **B&C**. Pain relief assessed 30 minutes after each dosing regimen for tail flick response (B) and paw withdrawal on hot plate (C). N = 12 mice. (Veh = vehicle; MPE = maximal protection efficacy).

2.2.4 Animal modeling for prostate cancer interception

The Lu lab reported inhibitory efficacy of AGN ethanol extracts (provided by a collaborator laboratory) on AR-negative DU145 and PC3 human PCa xenografts in athymic nude mice [11] with 100 mg/kg AGN (i.e., 2.5 mg per 25-g mouse). In a more recent study [13], they reported a dose-dependent suppression of the growth of AR-positive LNCaP-AR s.c. xenografts in NSG mice with daily gavage dosage of 5 mg and 10 mg AGN per mouse (~200 and 400 mg/kg body weight) starting 1 week before cancer cell inoculation (**Fig. 7B**), without any adverse effect on mouse body weight (**Fig. 7A)** (n=10, mean +SD) or the weight of the prostate [13]. In this model, metastasis to lung and liver is detectable by *ex vivo* bioluminescence of the harvested organs (**Fig. 7C**) and the metastasis incidence was decreased by AGN. Others reported D and/or DA each suppressed growth of sarcoma [14] or lung cancer [8 15] and colon cancer metastasis to lung [16] in syngeneic mice. Collectively, existing animal cancer models support broad-spectrum anti-cancer/metastasis activities of AGN.

Blood PSA reflected tumor burden after AGN treatment in mouse LNCaP-AR xenograft models. PSA is a human prostate specific protein and is not expressed by the mouse host. To determine whether AGN treatment affected PSA in the LNCaP-AR tumors from the above-referred experiment, the Lu lab staff measured the plasma PSA by ELISA and plotted against final tumor weight (**Fig. 7D**). The regression lines of the vehicle-treated tumors vs. AGN (10 mg group)-treated tumors were superimposable. Immunohistochemistry (IHC) staining for AR (nuclear) and PSA (cytosolic) did not show any reduction of these proteins in the cancer cells of AGN treated mice (**Fig. 7E**). Therefore, the blood PSA level in the tumor bearing mice with AGN treatment is a reasonable readout for PCa burden. This was further confirmed in the LNCaP xenograft model with decursinol (**Fig. 8**).

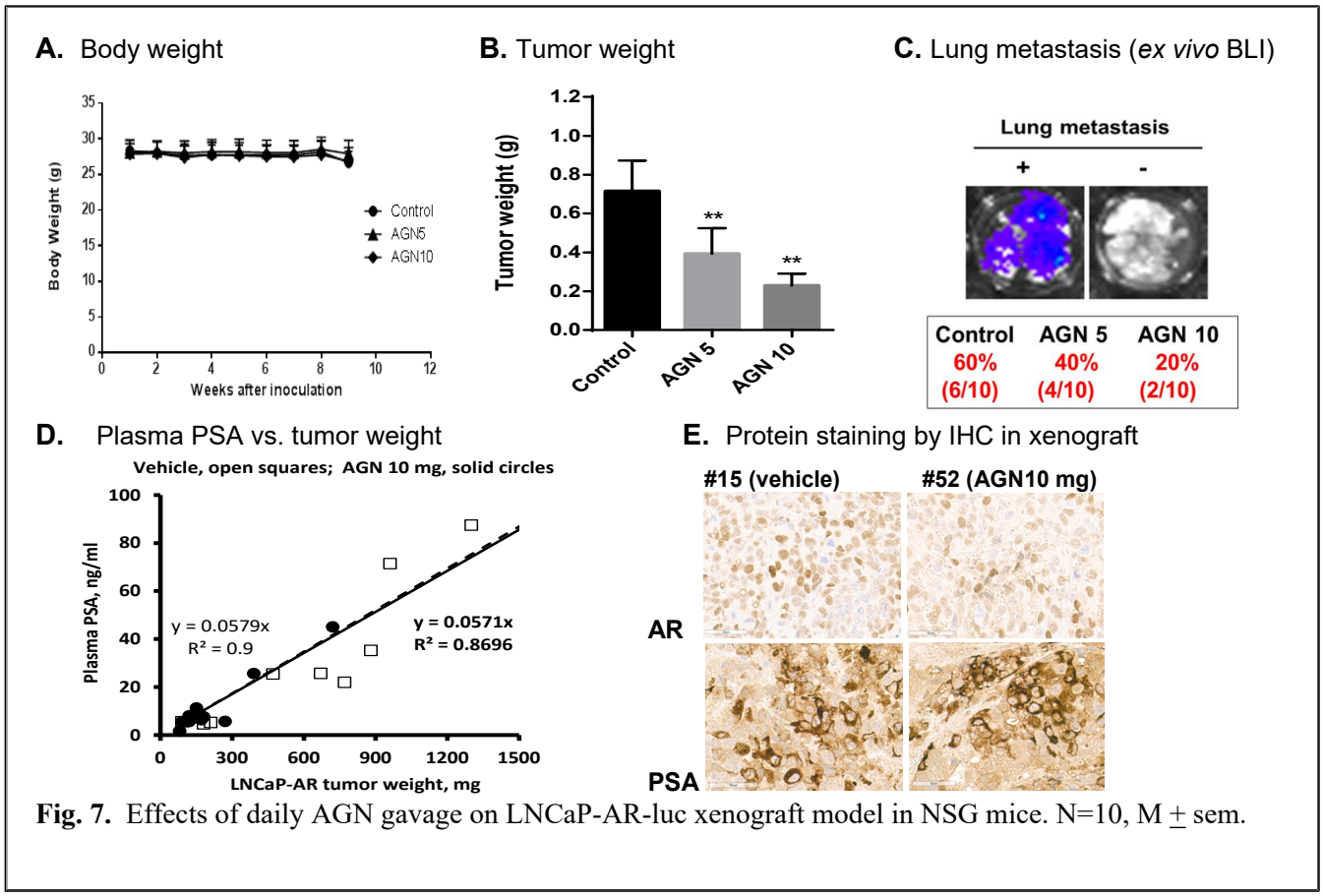


Fig. 7. Effects of daily AGN gavage on LNCaP-AR-luc xenograft model in NSG mice. N=10, M ± sem.

Blood PSA as a reliable readout for PCa interception by decursinol in s.c. LNCaP recurrent cancer interception model: Male NSG mice were inoculated on their right flank with LNCaP cells s.c. (1 million) in Matrigel. When tumor volume reached average of ~ 100 mm^3, tail vein blood was taken for baseline serum PSA by ELISA. Mice were then gavage-treated with vehicle (n=6 mice) or decursinol 3 mg per 25-g mouse (n=7 mice) daily. Mice were sacrificed after 4 weeks of treatment. Blood was taken for post-treatment PSA. Tumor and prostate were dissected and weighed. **Results** show that decursinol did not affect body weight of the mice, but significantly reduced the tumor volume (**Fig. 8A**) and weight (**Fig. 8B**). Decursinol (DOH) did not affect the weight of the prostate (**Fig. 8B**), affirming a distinct mechanism of action from ADT castration drugs that would have reduced the prostate weight. The post-treatment serum PSA showed a significant and tight linear correlation with the final tumor weight after necropsy for mice in the vehicle group (R^2=0.9386, n=6) (**Fig. 8C**). The majority of the decursinol-treated tumors weighed less and segregated along the PSA/weight regression line (considered as "responders"), whereas a couple of "non-responders" released PSA into blood in a quantity higher than predicted from the regression line (**Fig. 8C, solid circles**). IHC for AR and PSA did not detect any reduction of either protein in the responder and non-responder tumors vs. vehicle control tumors (not shown). These xenograft studies with PSA-indexed human PCa cells provide mechanistic justification for the use of blood PSA response in human patients in the proposed new trials to gauge the cancer control merit without confounding of the AR-PSA axis.

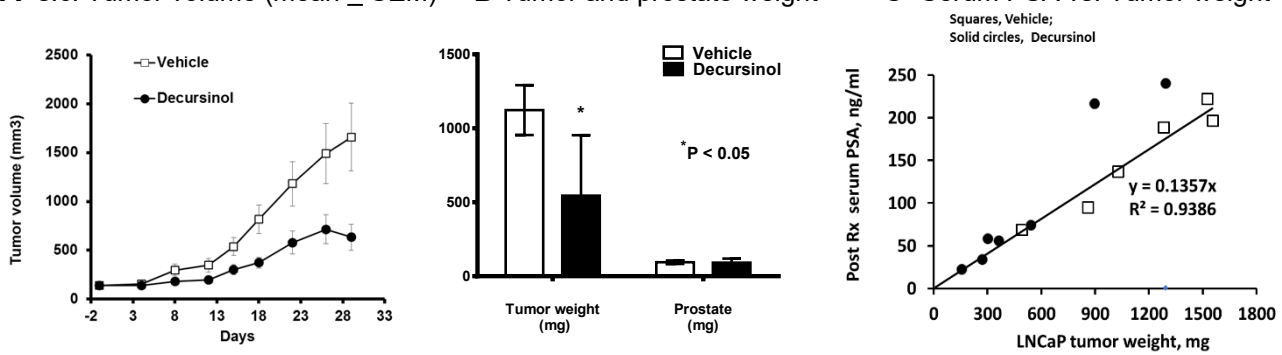


Fig. 8 Effects of daily gavage of decursinol (DOH) (3 mg per 25 g body weight or 120 mg/kg) for 4 weeks on LNCaP s.c. xenograft tumors in NSG mice. N=6/7, m ± sem. Regression line in **Panel C** was based on vehicle group only.

2.3 Study Rationale

Provide the scientific rationale for the research.

As illustrated in Fig. 4, the activities of the CYP enzymes (as governed by their metabolizer genotypes) could be a key determinant for their metabolic capacity that would deflect the D, DA and DOH dose response from linearity. Given the dose-dependence nature of the AGN efficacy to suppress prostate cancer (PCa) growth in animal models [13] (Fig. 7), we hypothesize dose proportionality of PK exposure metrics in humans. We therefore propose a PK trial (Aim 1 of NCI grant) to test PK exposure metrics as a function of increasing dosages of AGN-CognI.Q to probe any metabolic ceiling, thereby to guide decision whether dose-escalation in Phase I trial (NCI grant Aim 2A) will need to go to the maximal tolerated dose (MTD) or physical cap (10 capsules per dose) or to a dose lower than MTD but able to sustain a plateauing circulating pyranocoumarin level. The novel data will be exportable to disease prevention and therapy applications to other cancers and beyond oncology. Above all, there is no published, systematically collected data in humans for the acute or chronic use safety of AGN-CognI.Q at dosages above the current recommended herbal supplement dose for memory health or pain killing. The acute single dose safety metrics will serve as the primary endpoint for this protocol to ensure patient safety/protection is always the top priority of our research. Our preliminary PK data showed a DOH peak at 4-5 hours post each dose and the DOH peak concentration showed a linear dose response in the tested range of 800, 1200, 1600 and 2000mg. In subject #009, the 1600mg dose and the highest dose of 2000mg achieved 2700 ng/ml and 3400 ng/ml, respectively. While this subject had shown no EKG changes for the first 3 doses, the highest dose was related to a non-specific T wave alteration in the EKG at 5 h after dosing. Notably, this subject had not reported any symptoms; and his EKG T waves returned to normal pattern at 24 h after dose when the DOH level dropped to nearly baseline. Considering the possible cause-effect relationship between the administration of 2000 mg AGN-CognI.Q leading to peak DOH level surpassing a critical threshold and EKG T wave changes, the 2000 mg dose will be eliminated from the study for future subjects.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Willingness and ability to give informed consent.
2. Agree to comply with all study procedures and attend all study visits to the best of their ability.
3. Male with age >=40 years.
4. History of prostate cancer diagnosis. Subjects with history of neuroendocrine or small cell prostate cancer will be excluded. Subjects are eligible if meet one or more of the below criteria:

   a) Patients treated forprostate cancer and no detectable disease on imaging and clinical determination are eligible for enrollment, regardless of risk category.

   b) Patients in the low-risk and favorable intermediate-risk groups who are not currently receiving any treatment or have declined any treatment.
5. Not on concurrent androgen deprivation therapy.
6. ECOG performance status 0-2.
7. Life expectancy of greater than 12 months.
8. Subjects must have normal liver and kidney function as defined below:
   - a) total bilirubin within normal institutional limits,
   - b) AST(SGOT)/ALT(SGPT) $\leq$ 2.5 X institutional upper limit of normal,
   - c) Creatinine within 1.5 ULN of institutional limits OR creatinine clearance $\geq$ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
   - d) Adequate bone marrow function (Hgb ≥ 9.0 g/dL, Platelets ≥ 100 x 10^9/L, absolute neutrophil count (ANC) of ≥ 1.5 x 10^9/L), except for subjects with a history of chronic benign neutropenia, where an ANC of ≥ 1.0 x 10^9/L are eligible.
9. Subjects must agree to use two medically accepted method of contraception and must agree to continue use this method while on the trial and through at least one week after the last dose of study drug. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD) known to have a failure rate of less than 1% per year, or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) withdrawal, spermicides only, or lactational amenorrhea are not acceptable methods of contraception.
10. Subjects must stop the CYP3A4 and CYP2C19 strong inhibitors or inducers (see Table 7) 2 weeks prior to the start of the study and during the study
11. Subjects currently taking herbal supplements containing AGN extract, including CognI.Q, Decursinol-50, Ache Action, Fast-Acting Joint Formula, EstroG-100/Profemin must discontinue these or any other supplements

containing these products 4 weeks prior to starting study drug.

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Subjects with distant metastatic cancer. Node positive prostate cancer patients are allowed after completion of treatment.
2. Subjects who are receiving chemotherapy, or oral TKI, or immunotherapy (checkpoint inhibitor).
3. Subjects who are receiving any other investigational agents.
4. Uncontrolled intercurrent illness that would limit compliance with study requirements.
5. All vulnerable patient populations.
6. History of New York Heart Association Class III or IV heart failure, history of a myocardial infarction within 6 months, any uncontrolled cardiac arrhythmia, or any other cardiac related problem that would be considered a contraindication for participation in the opinion of the treating physician.
7. Use of androgen deprivation therapy (ADT) or anti-androgen therapy including LHRH agonist, antagonist, GNRH analogs, and antiandrogens.
8. Subjects who are taking Warfarin/Coumadin.

Screen failure may be re-screened.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

A subject can be removed from study by any one of the following criteria:

- The Quality of Life Laboratories can no longer provide AGN-CognI.Q supplement
- Subject withdraws informed consent
- Unforeseeable accident, relocation, or disabling life event prohibits continuation of study participation

Participants are free to withdraw from participation in the study at any time.

In addition, the investigators have the right to withdraw a subject from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Any medical condition that the study physicians determine may jeopardize the subject's safety if he continues in the study.
- Subject non-compliance to adhere to protocol requirements including difficulty in swallowing capsules
- Relapsed or progressive disease necessitates (prohibited disease targeted) concurrent treatment
- Unacceptable toxicity definitively related to AGN-CognI.Q dose limiting toxicity (DLT). Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued receipt of study intervention would not be in the best interest of the participant

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Data collection: Every effort should be made to obtain information on subjects who withdraw from the study. The primary reason for withdrawal from the study or study drug discontinuation should be documented on the appropriate eCRF (electronic Case Reporting Form).

Replacement: Subjects who withdraw due to difficulty swallowing capsules will be replaced. Those who have completed fewer than the 3 required doses in the escalation series and without DLT will be replaced. However, these subjects will be included for DLT analysis. Subjects withdrawn due to DLT will not be replaced.

Follow-ups: Subjects removed from study for DLT, unacceptable AE or SAE will be followed until resolution or stabilization of the adverse event to grade 1 or baseline, whichever is lesser.

Other subjects who discontinue the trial early, not due to DLT, will be followed up in 4 weeks of discontinuation.

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.
- Information provided in this protocol, including the description of study procedures, compensation, and recruitment, needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, Study Recruitment" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Potential subjects will be identified and recruited from Urology and Medical Oncology Clinics at Penn State Cancer Institute at Milton S. Hershey Medical Center.

StudyFinder (http://studyfinder.psu.edu) will be also used for recruitment purposes.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

4.2.1 How potential subjects will be recruited.

Potential subjects will be identified from patients receiving care at the Urology and Medical oncology clinics of the Hershey medical center and Penn State Health. The study team will approach potential subjects to introduce the trial during or after their clinic visit.
The potential subjects may access StudyFinder using the link: http://studyfinder.psu.edu. If they are interested, they can click to "contact the study team" then provide their name, email address, phone number and notes. A study team member will be in touch with the potential subjects to schedule a screening appointment with a urologist or a medical oncologist at the Urology and Medical oncology clinics of the Hershey medical center and Penn State Health.

4.2.2 Where potential subjects will be recruited.

Urology and Medical Oncology Clinics of the Penn State Hershey Medical Center.
Each patient has his own private room, where the consent for the study occurs.

4.2.3 When potential subjects will be recruited.

During or after clinic visit with the urologists or medical oncologists' offices.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Study physicians will review patient history as part of clinic visit and briefly introduce the trial to the patient during or at conclusion of the visit. If the patient is interested in learning more about the trial, he is referred to a clinical study staff member. Screening will not begin until informed consent has been signed and dated.

5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.

- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.
Those subjects identified via StudyFinder will be scheduled a clinic visit. After conclusion of clinic visits, patients who express an interest about learning more about the trial will be referred to a clinical research staff. The consent process will be conducted in a private room at HMC.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Subjects will be informed by the study team administering the informed consent process that their care will not be affected regardless of their decision to participate or not in the trial.

Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The study team will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family members or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The patients and any accompanying family member if on hand will be given private time to read the document and discuss to decide. Those patients who have not made decision will be given a copy of the consent form to take home with them before making a final decision to participate or decline.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

N/A

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, or implied consent form)

N/A

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

N/A

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

N/A

5.4.3 Describe why the research involves no more than minimal risk to subjects.

N/A

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

N/A

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

N/A

5.5.2 Describe why the research involves no more than minimal risk to subjects.

N/A

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest. The service of a healthcare interpreter will be used.

5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable.

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable.

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable.

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable.

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol."

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

No PHI of those records that have been reviewed to determine potential edibility will be saved or stored anywhere. It will immediately be destroyed by placing it into a locked trash can identified as confidential and be destroyed per the institutions policies.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide reasons why this research could not practicably be carried out without access to and use of PHI.

Information will be obtained from the subject's electronic medical record if identified through approved recruitment methods to determine eligibility.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide reasons why this research could not practicably be carried out without the waiver or alternation of authorization.

The waiver is requested only for recruitment to identify potential subjects and determine subject eligibility. Given that patients scheduled for clinic visits is the potential recruitment population, access to medical records and clinical schedules is necessary to identify potential subjects.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

7.1 Study Design

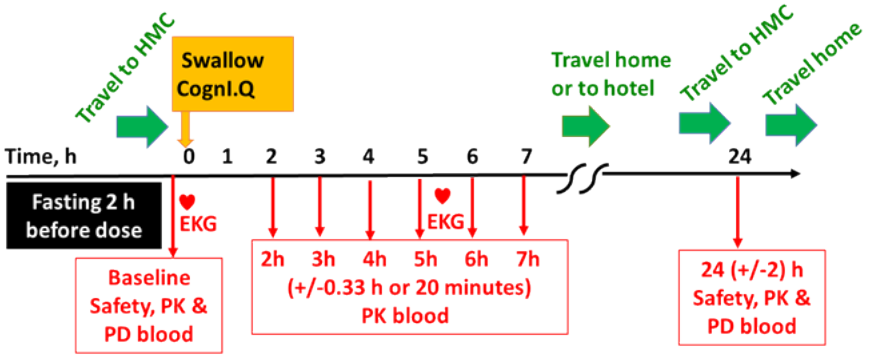
Describe and explain the study design.

Consented patients will be screened for physical exam and lab tests, and vital signs to establish eligibility (Visit 1, screening visit). Within 0-4 weeks of consent, eligible subjects will be scheduled for first dose PK blood collection and safety monitoring as indicated in Table 2 and flow chart schema below.

Table 2 Design for PK dose responses to AGN-CogniI.Q

Visit	PK Single dosage tested	Dosing form	AGN-CogniI.Q dosing/Food schedule
1	Screening visit	None	None
2	Dose level +1 (800 mg)	4 CogniI.Q capsules	Fast at least 2 h before dose and 1 h after
3	Dose level +2 (1,200 mg)	6 CogniI.Q capsules	Fast at least 2 h before dose and 1 h after
4	Dose level +3 (1,600 mg)	8 CogniI.Q capsules	Fast at least 2 h before dose and 1 h after
5	Follow up visit	None	None

Single ascending dose (SAD) PK Trial Design Scheme



Body Temperature and EKG will be monitored during PK blood collection period. Pre-dose baseline blood will be taken before subjects swallowing AGN-CogniI.Q capsules of any given dosage. Time starts when capsules have been swallowed.

Blood will be collected at a frequency guided by our published human PK study (PLOS One, 2015 [1]). Time points include pre-dose fasting baseline (0), 2 h (± 20 min), 3 h (± 20 min), 4 h (± 20 min), 5 h (± 20 min), 6 h (± 20 min), 7 h (± 20 min), and 24 (±2) h after dosing. The *AUC*- and C_{max}-dose curves for D, DA and DOH for each subject and all collectively (absolute and relative ratio to starting dose) will be evaluated for dose-linearity to inform any metabolic ceiling for dose-escalation and relationship to Cyp 2C19 and 3A4 metabolizer status.

Dose Limiting Toxicity:

A DLT is defined as an adverse event or clinically significant abnormal laboratory value listed in the table below that is assessed as, possibly, probably or definitely related to study drug, and is clearly unrelated to disease, disease progression, inter- current illness, or concomitant medications that occurs within the first 7 days of each treatment dose with AGN-CogniI.Q. NCI CTCAE version 5.0 should be used for all toxicity grading.

Table 3 Dose limiting toxicity of AGN-CogniI.Q

Toxicity ***	**Criteria for DLT graded by NCI CTCAE version 5.0**
Hematological	• Anemia, thrombocytopenia, or neutropenia of grade 2 and above for more than 5 days. • Chronic benign neutropenia with neutropenia of grade 2 and above is not considered as a DLT. • Grade 3 increased INR or prolonged PTT, or evidence of bleeding of grade 3 and above

Cardiac	• New onset of angina, new onset of symptomatic arrythmias, new onset of Atrial fibrillation or Atrial flutter, new onset of heart block, occurrence of myocardial infarction
Hepatobiliary	• Grade ≥2 total bilirubin for more than 5 days in absence of Gilbert's syndrome** • Grade ≥2 ALT or AST* for more than 5 days • Grade 3 serum alkaline phosphatase >5 days*
Gastrointestinal	• Grade ⩾ 3 nausea and/or vomiting ⩾72 hours despite optimal anti-emetic therapy • Grade ⩾ 3 diarrhea ⩾48 hours despite optimal anti-diarrhea treatment
Renal	• Grade ⩾3 serum creatinine for more than 5 days
Fatigue	• Grade 3 fatigue lasting > 5 days
Neurological	• Grade ≥3 neurological toxicities • Grade 2 neurological toxicities that do not resolve in 3 days with conservative management
Skin	• Grade 2 rash not subsiding to grade 1 after conservative management • Grade 2 itching not subsiding to grade 1 after conservative management • Other grade 2 skin condition due to drug, not subsiding to grade 1 post conservative management
*** Any DLT will result in participant discontinuation of study drug. Any redefined DLT will result in the reclassification of dosed subjects. **For Gilbert's syndrome a direct bilirubin will be measured * Repeat laboratory testing will be conducted to confirm clinically significant laboratory findings prior to designation as a DLT	

Justification of dosages

Animal modeling data: In animal studies performed by us in different PCa models [12] and by others in non-prostate cancer models, efficacious dose of decursin (D), decursinol angelate (DA) or decursinol (DOH) ranged from 2-3 mg of pure compounds per mouse per day. Assuming 2 mg per 25 g mouse, the human equivalent dose should be 2 mg/0.025 kg mouse/dose conversion factor of 12 = 6.7 mg/kg man. For a PCa patient weighing 75 kg, the dose we need to aim for should be 500 mg of D/DA per day. Each AGN-CognI.Q capsule contains 28 mg D/DA, therefore we need 17.9 capsules per day. Therefore, dose level +3 and +4 (4x - 5x current doses) would be target dose for escalation.

Practicality/feasibility for patients to swallow 10 AGN-CognI.Q capsules per administration (PK trial): In a Phase I trial at City of Hope [51], 28 dried white button mushroom powder tablets (500 mg each) were established as acceptable and feasible by similar patients to swallow in one day, 14 tablets in morning and 14 tablets in evening. The researchers did not find dose limiting toxicity (DLT), but did not escalate higher for MTD. In an Australian study of multiple phytochemicals in similar patients, 16 tablets/capsules were taken (8; twice per day) by participants with outstanding compliance [52]. Therefore, we justify 10 AGN-CognI.Q capsules per day will be

practical and acceptable for swallowing by our study subjects. The trial will provide practical knowledge of the feasibility of this dosage regimen for our patient cohort.

7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)
- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Research team will obtain vitals, administer EKG and take blood samples. Research team will observe the subject self-administer AGN-CognI.Q capsules. The subject will be dosed once every 7 (+7) calendar days. After the first subject is enrolled, a 14-day waiting period must occur between each subject before the next subject can be enrolled and dosed.

Treating research physicians will oversee past medical and cancer history, perform physical examination and ECOG PS. Management of any adverse events related to the study would be done as standard of care.

Research blood samples will be processed by authorized and trained lab staff at the Penn State Cancer Institute Laboratory of Immune Correlatives Mass spectrometry Core facility.

See study procedure and assessment in Appendix.

The data regarding demographics, medical history, concomitant medications, lab results etc. will be captured from electronic patient record. All AEs regardless of the relationship to the study drug and all grade 5 events will be captured and will be entered into Oncore.

1. The only data that will be entered for screen failures is data relating to demography, and the reason for the screen failure.
2. Every completed CRF is reviewed by the PI or physician on the study (sub-I) to verify the accuracy and completeness of the transcribed data from the source document(s). The PI acknowledges approval by electronically signing the CRF. Data entry timelines are as follows:

7.2.1. Visit 1 (screening visit)

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

Prior to registration, subjects will be evaluated during the Screening Period/visit (≤ 28 days prior to the initial administration of study intervention) to determine eligibility at Penn State's Clinical Research Center in Hershey. This visit may take up to 4 hours.

The following assessments will be performed during the Screening Period/visit (Day -28 to Day 0) and not expected to fast:

- Informed consent
- Assessment of eligibility
- Medical history/previous cancer history
- Physical exam
- Concomitant medications

- ECOG PS
- Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- Height and weight
- Baseline 12-lead EKG
- Complete Blood Count (CBC) with differential
- Complete Metabolic Profile (CMP)
- Coagulation tests (INR, PT, PTT)

Approximately 10 mL of blood will be needed for CBC with differential and CMP testing.

7.2.2 Visit 2

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

Visit 2 Day 1: the following assessments will be performed within 28 days from Visit #1 as baseline. This visit may take up to 10 hours.

- Concomitant Medications
- Focused physical exam based on elicited symptoms
- Vital signs, including BP, heart rate, respiratory rate and temperature
- CBC diff; CMP; coagulation tests (INR, PT, PTT (15 ml of whole blood) (Not needed if completed as part of the screening labs)
- 12-lead EKG
- Collect Research blood for PK and PD (immunology tests) (5 ml of whole blood in EDTA purple top tube) and DNA will be extracted from the buffy coat for CYP2C19 and 3A4 genotyping

Subjects will fast at least 2 hours before and one hour after taking the AGN-CognI.Q dose (800 mg, 4 capsules) with water. Subject are allowed to take all medications during the fasting period.

- At 2, 3, 4, 5, 6 and 7 h (± 20 minutes) following study intervention administration
  - Vital signs (blood pressure, heart rate, respiration rate, temperature)
  - Collect research blood for PK (5 ml of whole blood in EDTA purple top tube)
- 12-lead EKG at 5h (± 60 minutes) only
- Adverse event assessment

The following assessments will be performed on Visit 2 Day 2:

- At 24 h (± 2 h) following study intervention administration
  - Vital signs (blood pressure, heart rate, respiration rate, temperature)
  - 12-lead EKG
  - Collect Research blood for PK and PD (Immunology tests) (5 ml of whole blood in EDTA purple top tube)
  - Safety blood lab tests (CBC diff; CMP; coagulation tests (INR, PT, PTT), 15 ml of whole blood)
  - Adverse event assessment

A remote safety follow-up by phone on any AEs any time between Visit 2 and Visit 3.

7.2.3 Visit 3

Visit 3 Day 1: The following assessments will be performed 7(+7) calendar days from Visit #2. This visit may take up to 10 hours:

- Concomitant Medications
- Focused physical exam based on elicited symptoms
- Vital signs, including BP, heart rate, respiratory rate and temperature
- Safety blood lab tests (CBC diff; CMP; coagulation tests (INR, PT, PTT), 15 ml of whole blood) (may be obtained up to 5 calendar days prior to treatment day at Penn State Health system)
- 12-leads EKG
- Collect Research blood for PK and PD (immunology tests) (5 ml of whole blood in EDTA purple top tube)

Subjects will fast at least 2 hours before and one hour after taking AGN-CognI.Q dose (1200 mg, 6 capsules) with water. Subject are allowed to take all medications during the fasting period.

- At 2, 3, 4, 5,6 h and 7 h (± 20 minutes) following study intervention administration
  - Vital signs (blood pressure, heart rate, respiration rate, temperature)
  - Collect research blood for PK (5 ml of whole blood in EDTA purple top tube)
- 12-lead EKG at 5h (± 60 minutes) only
- Adverse event assessment

The following assessments will be performed on Visit 3 Day 2:

- At 24 h (± 2 h) following study intervention administration
  - Vital signs (blood pressure, heart rate, respiration rate, temperature)
  - 12-lead EKG
  - Collect Research blood for PK and PD (immunology tests) (5 ml of whole blood in EDTA purple top tube)
  - Safety blood lab tests (CBC diff; CMP; coagulation tests (INR, PT, PTT), 15 ml of whole blood)
  - Adverse event assessment

A remote safety follow-up by phone on any AEs any time between Visit 3 and Visit 4.

7.2.4 Visit 4

Visit 4 Day 1: The following assessments will be performed 7(+7) calendar days from Visit #3. This visit may take up to 10 hours:

- Concomitant Medications
- Focused physical exam based on elicited symptoms
- Vital signs, including BP, heart rate, respiratory rate and temperature
- Safety blood lab tests (CBC diff; CMP; coagulation tests (INR, PT, PTT), 15 ml of whole blood) (may be obtained up to 5 calendar days prior to treatment day at Penn State Health system)
- 12-leads EKG
- Collect Research blood for PK and PD (immunology tests) (5 ml of whole blood in EDTA purple top tube)

Subjects will fast from at least 2 hours before and one hour after taking AGN-CognI.Q dose (1600 mg, 8 capsules) with water. Subject are allowed to take all medications during the fasting period.

- At 2, 3, 4, 5, 6 h and 7 h (± 20 minutes) following study intervention administration
    - Vital signs (blood pressure, heart rate, respiration rate, temperature)
    - Collect research blood for PK (5 ml of whole blood in EDTA purple top tube)
- 12-lead EKG at 5h (± 60 minutes) only
- Adverse event assessment

The following assessments will be performed on Visit 4 Day 2:

- At 24 h (± 2 h) following study intervention administration
    - Vital signs (blood pressure, heart rate, respiration rate, temperature)
    - 12-lead EKG
    - Collect Research blood for PK and PD (immunology tests) (5 ml of whole blood in EDTA purple top tube)
    - Safety blood lab tests (CBC diff; CMP; coagulation tests (INR, PT, PTT), 15 ml of whole blood)
    - Adverse event assessment

A remote safety follow-up by phone on any AEs any time between Visit 4 and Visit 5.

7.2.5 Visit 5 or End of Treatment Visit (Safety assessment/follow up and washout PK/PD metrics)
The End of Treatment Visit is defined as 7 (-2) or 7 (+5) calendar days after last dose of AGN-CognI.Q. This visit may take up to 2 hours:

- Concomitant Medications
- Focused physical exam based on elicited symptoms
- Vital signs, including BP, heart rate, respiratory rate and temperature
- Safety blood lab tests (CBC diff; CMP; coagulation tests (INR, PT, PTT), 15 ml of whole blood)
- 12-leads EKG
- Collect Research blood for PK and PD (immunology tests) (5 ml of whole blood in EDTA purple top tube)
- Adverse event assessment

7.2.6 Follow up at 4 weeks (± 7 calendar days) following last dose.
Remote follow up by phone to review any AEs

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Approximately three (3) months (including 1 screening visit and 4 study visits and 4 remote follow ups)

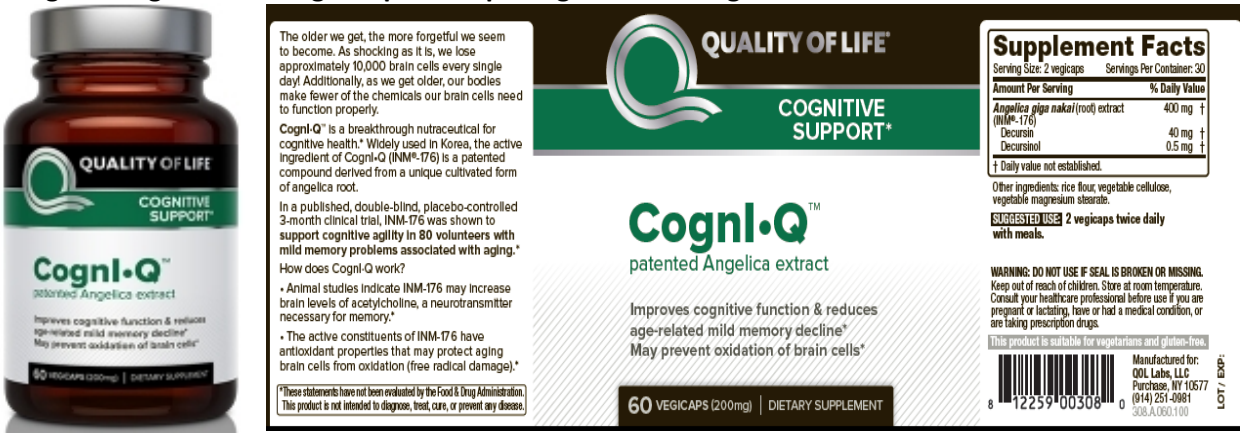
7.4. Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1. Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

The AGN-CognI.Q herbal supplement product (CognI.Q) (**Fig. 9**) for the proposed human clinical trials in prostate cancer patients will be purchased in bulk from Quality of Life Labs/Maypro (Purchase, NY). CognI.Q capsules are currently marketed as a dietary supplement for memory health through QOL website or phone/mail order or Amazon.

Fig. 9 Image of AGN-CognI.Q product package and labeling information.



CognI.Q capsules (vegicaps), 200 mg INM-176 AGN per each.
Other ingredients: rice flour, vegetable cellulose, vegetable magnesium stearate

Physical appearance of the capsules. **Smell**: medicinal herbal scent

The ingredient supplier Scigenic Inc. uses a proprietary technology to extract AGN with ethanol and powderize with cellulose to a finished granular powder product that is 1/5 the weight of the raw herbal root (INM-176). This product was chosen because its close match with the AGN extracts that had been studied in the TRAMP model in the phytochemical profiles. This product was purchased from Quality of Life Labs for the first-in-human PK study of pyranocoumarins (Zhang et al, PLOS One 2015) [1].

The INM-176 batches and finished marketable supplement products (e.g., CognI.Q) are routinely tested and pass for heavy metals (Lead, Cadmium, Arsenic and Mercury) (Table 3) and microbials (yeast count and mold count; *staphylococcus aureus*, *E. coli* and *Salmonella*) (Table 4).

Products testing results (per Quality of Life Labs)

Table 4. Heavy metal testing

Heavy Metals	Found(mcg/day)	Limit (mcg/day)
Lead	0.01	10
Cadmium	0.008	5
Arsenic	0.104	15
Mercury	0.002	15

Table 5. Microbiological testing results

Microbial Tests	Limit (cfu/gm)	Result	Status
Aerobic Plate Count/gm:	NMT 20000	<20000	pass
Yeast count & Mold Count/gm	NMT 2000	<2000	pass
Presence of Pathogen/gm			

Staphylococcus aureus	Absent	Absent	pass
Escherichia coli	Absent	Absent	pass
Salmonella species	Absent	Absent	pass

Quality of Life Labs website (http://qualityoflife.net/product/212/Cogni-Q%E2%84%A2.html)

7.4.2. Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

This is a single dose, dose escalating trial using AGN-CognI.Q capsules. Subjects will begin at dose level +1. Each dose level is a one-time dose. Subjects will take the next dose on next study visit, usually a week apart (7 (+7) calendar days). If a subject develops any SAE related to study drug that is considered life threatening, requires hospitalization or results in a disability/incapacitation, or a DLT, the subject will stop taking AGN-CognI.Q. Strong inhibitors and strong inducers of CYP3A4 and Cyp 2C19 be prohibited two weeks prior to and during the treatment. Protocol procedures not completed due to weather, holidays or weekends, participant's vacation up to delay of one week, or drug related adverse event, will not be considered deviations.

Oral, swallow with water.

A single dose of prescribed number of AGN-CognI.Q capsules (See Table 2) will be self-administered by the subject during the research visit at the direction of the research team.

Any number of capsules rejected due to swallowing or vomiting will be replaced to make up the full prescribed dosage for a given PK visit.

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

Open label. No randomization.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

The swallowing of the prescribed number of capsules for a given visit will be supervised by clinical research staff. No dosing at home. Any missed number of capsules due to swallowing or vomiting will be replaced to make to full prescribed dosage for that visit.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

No blinding.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

AGN-CognI.Q capsules in bulk packaging will be shipped to HMC IDS.

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

In locked container/cabinet at Room temperature, away from direct sun light.

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

AGN-CognI.Q capsules, each containing 200 mg INM-176 AGN extract, will be dispensed by HMC IDS. Clinical research staff will supervise subjects to swallow prescribed number of capsules for a given visit. Any rejected number of capsules due to swallow failure will be replaced until the completion of the dosage required for that visit.

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

Any unused capsules returned will be counted and noted for participant compliance and disposed by HMC IDS.

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

Concomitant medication including herbal and vitamin supplements within 30 days prior to starting the IP collected. Any required medications for medical care would be allowed. Strong inhibitors and strong inducers of CYP3A4 and CYP2C19 be prohibited two weeks prior to and during the treatment.

8.0 Number of Subject and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

At least twelve evaluable subjects are needed to complete this PK study. Twenty patients will be consented, considering screen failures and subject dropouts.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

For PK trial, *N≥ 12 patients recommended by FDA. (*Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry 2019)*.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

Primary endpoint (safety metrics): The frequency and type of adverse effects (clinical observations) will be reported per CTCAE version 5, separately for each of the 4 dose levels and tested for their dose dependence. The highest dose-level a subject can tolerate or is willing to take will be summarized. Summary statistics (mean, median, standard deviation, box plot and frequency distribution) will be provided for AEs and blood lab tests. Linear mixed effect model will be used to evaluate the association between pretreatment/baseline blood safety data and different AGN Cogni.Q dose levels (across different visits), using regression methods. Data from multiple visits will be analyzed using linear mixed-effect models to account for the longitudinal data structure.
PK Metrics: The relationship between PK metrics of AGN pyranocoumarins and AGN doses will be summarized graphically. Appropriate regression analyses will be used to model the effect of increased dose level. For example, in PK dose-exposure data (absolute and relative ratio to starting dose), the AUC and C_{max} at 4 different dose levels will be modeled as $Y = b_0 + b_1 dose^a + error$, where parameter a substantially smaller than 1 would indicate a strong diminishing return of dose on $\mathrm{Y\ (AUC\ or\ Cmax)}$.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

The study will be conducted with guidance with the Penn State Cancer Institute's (PSCI) Data Safety Monitoring Plan (DSMP). The PSCI DSMB will review the following per their charter:

- Adverse event summary
- Audit results, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

Results and recommendations from the review of this report by the DSMC will then be provided to the principal investigator in a DSMC review letter. The principal investigator will address the concerns. The principal investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

PI will review the safety data periodically.
Safety data

1. Clinical safety/toxicity according to NCI Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

- Adverse event summary report (of above metrics)
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Safety is assessed by three types of metrics below and will be reported on the case report form (CRF).

1. Safety lab collection
2. PK collections
3. EKG

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Data will be collected at the following timepoints:

- At baseline,
- 0, 2, 3, 4, 5, 6, 7 hours post AGN-CognI.Q administration,
- 24h after each dose,
- 7 (-2) or 7 (+5) days after last dose,
- 4 weeks (± 7 days) after last dose,
- A phone follow-up to assess adverse events obtained any time prior to next treatment day, 7 (-2) or 7 (+5) calendar days after last dose, or 4 weeks ±7 calendar days after last dose.

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

PI Dr. Monika Joshi and Penn State Cancer Institute DSMB per PSCI's Data Safety Monitoring Plan (DSMP).

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Each subject's data will be discussed by the PI and appropriate staff at weekly meetings and prior to dosing. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Studies have been reported in the use of AGN-CognI.Q have low rates of systemic reaction (mild GI issues nausea/dyspepsia and anorexia 4-8%) and very rare severe reactions. Data will be reviewed monthly and if any reactions occur in that time frame, the set will be given to the statistician to determine if rates are the same or above reported rates.

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

After the first subject is enrolled, a 14-day waiting period must occur between each subject before the next subject can be enrolled and dosed. If one subject develops a DLT (Section 7.1, Table 3) at any dose level, that subject will cease treatment but will continue safety assessments follow-ups. If a second subject develops a DLT at the same dose level, the trial will be stopped and the dose level below will be the MTD. Any subjects who are at higher dose level at the time of 2nd DLT occurrence, will also stop with no further escalation. All subjects will start at the 800 mg dose (visit 2). Each subject will continue to the next week's dose until a DLT has been reached. However, if 2 DLTs occur at the starting 800 mg dose level, trial will be suspended.

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

Risk of participating in the trial include a) those associated with clinical procedures of obtaining specimens; b) unanticipated adverse effects of AGN-CognI.Q use at higher than currently recommended dietary supplement dose; and c) interactions of AGN-CognI.Q with concurrent medications. These are discussed below:

Clinical procedure risks. Venipunctures will inflict temporary superficial pain. Venipunctures may occasionally lead to localized hemorrhage and bruises at site of needle insertion Occasionally, a subject may experience fainting spell during the blood draw. An IV line is also known as a cannula, angiocatheter, may become blocked, leak fluid into the skin or cause infection.

AGN-CognI.Q supplement risks: Based on reported adverse events in the Korean Phase II study of 3 months duration of supplement at the dose 800 mg per day (See **Table 6** below) (Kim et al, "A three month placebo-controlled clinical trial of INM 176 in the old aged subjects with memory impairment." *Journal of Korean Neuropsychiatric Association*, 42:254-262; 2003), anorexia, nausea and indigestion events might be potential events to assess for possible link to AGN-CognI.Q (INM176) use, especially when the dosage is increased to 10 capsules per self-administration.

Table 6 "Adverse events in elderly Koreans taking 800 mg AGN supplement (INM176™) vs. placebo for 3 months."

Adverse Event	INM176 group	Placebo group
	N=49	N=43
Anorexia	3 (6.1%)	0 (0%)
Nausea	3 (6.1%)	1 (2.3%)
Dyspepsia	4 (8.2%)	1 (2.3%)
Dizziness	2 (4.1%)	3 (7.0%)
Sedation	4 (8.2%)	3 (7.0%)
Itching sense	3 (6.1%)	3 (7.0%)

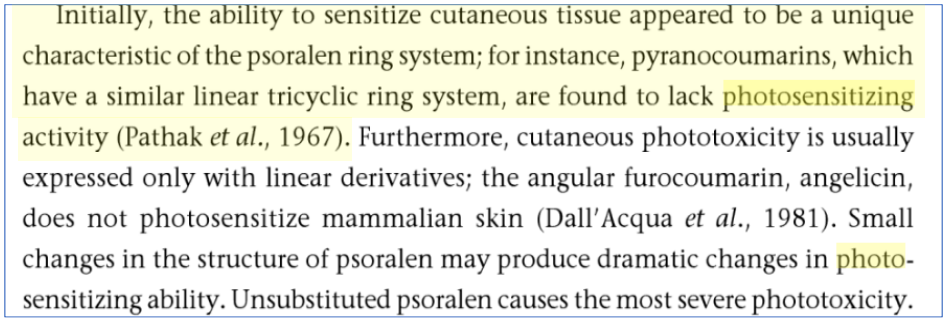
From Kim et al, J Korean Neuropsych Assn 2003.

In addition, Safety information from a clinical trial in healthy men in Hershey Medical Center **(**NCT03630328, PI Lu https://clinicaltrials.gov/ct2/show/NCT03630328?term=cogni.q&rank=1**)** has been collected. Still "blinded" for study rigor, not a single adverse event was reported by the 15 subjects, nor was any clinically-significant change of liver and kidney integrity blood chemistry indices, affirming the safety of both AGN supplement and placebo capsules to subjects in US.

The detailed safety monitoring plan during PK blood collection was designed to assess single dose-associated AE, which will also inform Phase I/II safety assessment for the chronic supplement use for up to 6 months.

A recent animal studies of decursinol for pain relief (See previous data section Fig. 6), a reduction of rectal temperature closely tracked the efficacy of thermal pain alleviation in both intensity and time course. This metric will be incorporated in our trial as another potential PD biomarker and could be beneficial as a fever-reduction herbal remedy in addition to other health benefits.

Photosensitivity related to coumarins Older literature suggested furanocoumarins such as psoralen or derivatives, with potential to enhance photosensitivity. (Dermatotoxicology, 6th ed. 2004). A relevant excerpt is shown below.



Initially, the ability to sensitize cutaneous tissue appeared to be a unique characteristic of the psoralen ring system; for instance, pyranocoumarins, which have a similar linear tricyclic ring system, are found to lack photosensitizing activity (Pathak *et al.*, 1967). Furthermore, cutaneous phototoxicity is usually expressed only with linear derivatives; the angular furocoumarin, angelicin, does not photosensitize mammalian skin (Dall'Acqua *et al.*, 1981). Small changes in the structure of psoralen may produce dramatic changes in photo-sensitizing ability. Unsubstituted psoralen causes the most severe phototoxicity.

Natural AGN pyranocoumarins were noted to lack such activity.

One current subject in this study exhibited transient, non-specific T wave alterations without experiencing any symptoms. Restlessness (Grade 1) was reported by one current subject after the first dose of the study drug. This adverse event was unexpected and is considered possibly related to the study drug. subject recovered without the need for additional intervention.

The risk to study subjects is judged to be reasonable due to single dose exposure per week. This study includes detailed safety assessment by clinical observations (vitals, EKG tracing, and NCI Common Terminology Criteria for Adverse Events [CTCAE version 5.0]) and blood labs (chemistry for liver and kidney function, hematology/cytology) at 0h, and 24 h after each dose and 7 days after the last dose. The PK study will not proceed to the next higher level if safety outcomes do not warrant dose escalation per section 9.8 Suspension of Research.

Risks associated with herbal interactions with concurrent medications:

Use of ADT or anti-androgen therapy including LHRH agonist, antagonist, GNRH analogs, antiandrogens like bicalutamide, nilutamide etc. are not permitted on the study.

Given published data of pyranocoumarin metabolism by CYP isoforms (Zhang *et al,* 2015, [2]) and that ~ 60% of clinically used drugs are metabolized by CYP3A4 and ~ 10% by CYP2C19, subjects must stop the CYP3A4 and CYPC19 **sensitive substrates**, **strong inhibitors,** or **strong inducers** of the respective CYP isoforms (per FDA web site https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers). (See **Table 7** below).

CYP isoform	Sensitive Substrates	Strong Inhibitors	Strong Inducers
CYP2C19	**S-Mephenytoin** (Anti-convulsant) **Omeprazole** (Prilosec; Proton pump inhibitor)	**Fluconazole** (Anti-fungal) **Fluoxetine** (Prozac, SSRI-antidepressant) **Fluvoxamine** (Luvox, SSRI-antidepressant) **Ticlopidin** (Ticlid, anti-thrombotic)	**Rifampin** (Anti-biotic)
CYP3A4	**Alfentanil** (Opioid) **Avanafil** (ED drug) **Buspirone** (Anxiolytic) **Conivaptan** (Vaprisol, peptide inhibitor for vasopressin) **Darifenacin** (Bladder control) **Darunavir** (Anti-viral, HIV) **Ebastine** (Anti-histamine, 2nd gen) **Everolimus** (mTOR inhibitor) **Ibrutinib** (Tyrosine kinase inhibitor TKI) **Lomitapide** (Cholesterol drug) **Lovastatin** (Cholesterol drug) **Midazolam** (Anxiolytic; benzodiazepine) **Naloxegol** (Opioid blocker) **Nisoldipine** (Hypertension drug) **Saquinavir** (Anti-viral, HIV) **Simvastatin** (Cholesterol drug)	**Boceprevir** (Anti-viral, HIV) **Cobicistat** (Tybost, Cyp3A4 suicide inhibitor; combo with anti-HIV drugs) **Danoprevir and Ritonavir (**Anti-virals combo, HIV) **Elvitegravir and Ritonavir (**Anti-virals combo, HIV) **Grapefruit juice** (beverage/food) **Indinavir and Ritonavir (**Anti-virals combo, HIV) **Itraconazole** (Anti-fungal) **Ketoconazole** (Anti-fungal) **Lopinavir and Ritonavir (**Anti-virals combo, HIV) **Paritaprevir and Ritonavir** and (**Ombitasvir and/or Dasabuvir**) **(**Anti-virals combo, HIV) **Posaconazole** (Anti-fungal) **Ritonavir** (Anti-viral, HIV)	**Apalutamide** (Androgen blocker, prostate cancer drug) **Carbamazepine** (Anti-convulsant) **Enzalutamide** (Androgen blocker, prostate cancer drug) **Mitotane** (Lysodren, andrenocytolytic drug, cancer drug) **Phenytoin** (Anti-convulsant) **Rifampin** (Anti-biotic) **St. John's wort** (herbal supplement)

	Sirolimus (mTOR inhibitor) **Tacrolimus** (Fujimycin, Prograf, immunosuppressant, HVGD) **Tipranavir** (Anti-viral, HIV) **Triazolam** (Anxiolytic; benzodiazepine) **Vardenafil** (ED drug)	**Saquinavir and Ritonavir (**Anti-virals combo, HIV) **Telaprevir** (Anti-viral, HIV) **Tipranavir and Ritonavir (**Anti-virals combo, HIV) **Telithromycin** (Anti-biotic) **Troleandomycin** (Anti-biotic) **Voriconazole** (Anti-fungal)	

Particularly relevant to older male patients, some of the listed drugs are commonly used for managing blood cholesterol (e.g. Statins), ED drugs avanafil and vardenafil, hypertension, and heart-burn acid blocker proton pump inhibitor drug omeprazole (Prilosec). In addition, some are cancer therapeutic drugs (next-gen androgen receptor drugs enzalutamide and apalutamide; mTOR inhibitors everolimus, sirolimus; TKI drug ibrutinib/venetoclax), anti-biotics, and anti-fungals. Many are novel anti-virals for HIV/AIDS.

No data for drug-drug interactions with AGN or its pyranocoumarins in human is available at the present. For practical purpose of the proposed trials, subject should not use grapefruit juice (high in furanocoumarins) and St. John's wort supplement.

For more comprehensive knowledge of pyranocoumarin metabolism in relation to safety/toxicity and PSA controlling efficacy of Cogni.Q, we propose to genotype these key Cyp isoforms as we have done previously (Zhang J 2015, [2]) from each patient to correlate with their PK metrics for D, DA and DOH as well as PSA response outcome. Such CYP and PK information could be important in stratification of patients in future trials.

Psychological, financial, legal risk assessment:
No increased risk in these categories by participating in this study. Psychological reward might be a positive factor of participating in our study as most people derive pleasure by knowing study results may benefit themselves and many others. Financial loss due to missed work is partially mitigated by our subject remuneration plan (see section 13.0).

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 14.0.

There is no direct benefit to subjects. Potential benefits from the supplement may include potential immune enhancement, pain killing, and cognitive improvement (against memory loss). While the single dose of AGN-CognI.Q per week will not likely exert lasting anti-cancer impact, the subjects may benefit from the immune enhancement bioactivity that will be explored as potential PD biomarkers after each single dose in this trial.

11.2 Potential Benefits to Others

Include benefits to society or others.

Benefits from this PK dose trial will be important data to fill several key gaps of knowledge about the practical use of the supplement that can facilitate design and conduct of not only this Phase I/II trial, but also oncology studies in other organ sites as well as other health benefits, including potential immune enhancement, pain killing, and cognitive improvement (against memory loss) in populations who are similar in age to the studied subjects. The PK Dose-response (linearity) information may benefit future use of AGN-CognI.Q supplements in research participants and others for cancer prevention control and other health conditions.

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

The data of the study will not be shared with the subjects.

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Subject/patient will be paid $100 for screening visit if the subject is eligible for the study. Each subject will be compensated $400 for each PK visit completed (each PK visit lasts two days, Day 1 $300; Day 2 $100, for a total of 4 PK visits). An additional $100 is paid for each subject for a 7 (-2) or 7 (+5) calendar days post-last dose safety follow-up visit. The grand total is $1400 if a subject completes all 5 visits. Payment will be made after each visit. Payment is not by a cumulative lump sum after all visits. Subject will be allowed up to three overnight hotel stays if subject's home address is in 50 miles or more away from Penn State Hershey Medical Center. The sponsor will secure the hotel rooms for these subjects.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

The lab test cost of the CBC diff, CMP comprehensive metabolic panel as well as research labs that are required for determination of eligibility and safety will be paid by the study budget. These tests are being done for research purpose only and will not be billed to the subjects or their insurance company.

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

PSCI CTO will provide regulatory support and Data and Safety Monitoring.

All screening visit and research visits will be conducted at Penn State Hershey Medical Center.

Safety blood lab tests will be routed to Penn State Hershey Medical Center clinical labs.

Research blood samples will be processed by authorized and trained lab staff at the Penn State Cancer Institute Laboratory of Immune Correlatives and Mass spectrometry Core facility (College of Medicine Main Building) and Department of Pharmacology labs.

Department of Pharmacology will provide budgetary and financial management support.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

Approximately 3500 prostate cancer patients are under the care of urological, radiation and medical oncologists at the PSCI Hershey campus. We estimate annually ~ 50 post-RP/RT patients would be eligible for recruitment to the proposed trial and 3 patients could be enrolled each month.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

Dr. Joshi will devote 15% of her time to thie project. She will be in charge of all matters of IRB compliance, trial supervision and management, patient safety assessment, regulatory and reporting, efficacy testing.

She will collaborate with Dr. Jay Raman (5%), in patient recruitment and assessment. A combined effort for clinical trial leadership is 20%.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

Medical or psychological resources at Penn State College of Medicine are available as needed. Subjects will be financially responsible for utilization of any resources.

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

Monthly in person/zoom meetings will be conducted. Weekly email updates will be sent to ensure the team stays well informed. Additional emails or other electronic media communications will be disseminated as needed.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

FDA IND (Investigational New Drug) approval has been granted as of May 13, 2022.

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** Use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use (remnant samples only).

☐ Clinical Research Center (CRC) Advisory Committee – **University Park** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves radiation procedures. After completion of coverage analysis by the Clinical Trials Office, all research involving radiation procedures (standard of care and/or research-related) requires upload of "HRP-903 - Radiation Review Form" in CATS IRB.

☒ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

☐ St. Joseph Administrative Review – Penn State Health only – Penn State Health Research that will involve St. Joseph Medical Center or St. Joseph Community Medical Groups, their patients, or their medical records.

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

Not applicable. No other site.

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Not applicable.

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable.

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable.

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable.

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable.

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

18.2 Recording of Adverse Events

Address the frequency and process for eliciting adverse event information from research subject, e.g., "Research subjects will be routinely questioned about adverse events at study visits."

In the response, incorporate the following as written:
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy **NOTE:** Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as medical history and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

The study team will record all adverse events with start dates occurring from the start of the study drug until follow-up visit by telephone after the last day of the study drug. SAEs will be followed until resolution or stabilization. All SAEs will be reported to the sponsor within 24 hours of knowledge.

SAEs will be reported to the sponsor using the MedWatch Form 3500A. Updates to the SAE should be made as events change.

Any subject who experiences a DLT will be withdrawn from the treatment but will continue safety assessment follow-ups.

All AEs regardless of the relationship to the study drug and all grade 5 events will be captured and will be collected and entered into Oncore.

All AEs (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

All abnormal lab values will be reviewed for clinical significance by the research physician. Those that are determined to be clinically significant will be recorded as AE's.

18.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

The Sponsor Dr. Lu and/or his sponsor proxy will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written:
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor will notify the responsible review division of the FDA of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) possibly or probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.6 Unblinding Procedures

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

Not applicable. This is an Open label study.

18.7 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

Stopping Criteria:

- Any SAE related to study drug that is considered life threatening, requires hospitalization or results in a disability/incapacitation.
- DLT.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Describe how you will ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

It is the responsibility of the principal investigator to ensure that the rights and well-being of study participants are protected, that the reported study data is accurate, complete, and verifiable, and that the study is conducted and biological specimens collected in compliance with the currently approved protocol or amendment, with institutional and IRB policies, with International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and with any other applicable regulatory requirements (including Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP)). The PSCI Quality Assurance (QA) will provide clinical trial monitoring services for this study, which is an independent review of the regulatory and participant records and associated data collected to assure appropriate compliance, ensuring human subject's protection, examine the quality, reliability, and integrity of data collected and provide opportunities for corrective action while the study is ongoing.

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

19.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Indicate the process for identifying, recording and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member's role in the adverse event reporting process. Include the following if applicable:

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

Any DLTs will be reported to DSMC (PSCI-DSMC@pennstatehealth.psu.edu) for review by study Medical Monitor within 5 days of awareness.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, sponsor and/or DSMB of all Unanticipated Problems/SAEs.

The Monitor will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

Reportable AEs, UAP, SAEs and Protocol Violation reporting to DSMC

Type of Event	To whom will it be reported	Time Frame for Reporting	How to report?

Death of a research participant unless the death is expected (e.g., due to disease progression).	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 24 hours	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu
Serious Adverse Event, *regardless of relatedness of expectedness*	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 10 working days from the time the study team received knowledge of the event.	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu
Unanticipated Problems that are not adverse events or protocol deviations	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 10 working days from the time the study team received knowledge of the event.	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Not applicable.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Not applicable.

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

Not applicable.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Not applicable.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

Not applicable.

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not applicable.

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

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22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

This research is conducted at Penn State Health and College of Medicine. See "HRP-598 Research Data Plan Review Form".

For research being conducted at Penn State Health or by Penn State Health researchers only: The research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form Application Supplement."

In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all sub-sections of section 22.

For all other research: complete the following section. Please refer to PSU Policy AD95 for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be carried out locally and meets applicable requirements. If you have questions about Penn State's Policy AD95 or standards or need a consultation regarding data security, please contact security@psu.edu.

See the Research Data Plan Review Form

23.0 Appendix: Study Procedure and Assessment

Procedures / Assessments	Visit 1 Screening	Visit 2,3,4, AGN-CogniI.Q Dose 1-3 7 (+7) calendar days			Safety follow-ups prior to Visit 3, 4, 5 [f]	Visit 5 End of treatment	Follow-up
	Days –28 to 0	Day 1 [b] pre-dose	Day 1[b] post-dose	Day 2		7 (-2) or 7 (+5)[b] calendar days after last dose	4 weeks (± 7 calendar days) [b] after last dose
Informed Consent [a]	X						
Assessment of eligibility (Inclusion/Exclusion)	X						
Medical/Cancer History & physical examination, weight and height	X						
Focused physical exam based on elicited symptoms		X				X	
Concomitant Medications	X	X				X	
Vital Signs (HR, temp, BP, RR)	X	X	@2, 3,4, 5, 6, 7 h ±20 min post dose	@24 ±2 h post dose		X	
ECOG Performance Status	X						
AGN-CogniI.Q treatment			X [e]				
12-leads EKG	X	X	@5±1 h post dose	@24 ±2 h post dose		X	
Safety Blood Lab Tests (CBC diff; CMP; coagulation tests (INR, PT, PTT)	X	X[c]		X		X	
Research blood-PK (5 ml each time point)		X	@2, 3, 4, 5, 6, 7 ±20 min	@24 ±2 h post dose		X	

			post dose				
Research blood-PD (Immunology tests, aliquot from 0 and 24 h PK blood)		X		@24 ±2 h post dose		X	
Research buffy coat (aliquot from 0 h PK blood)		X [d]					
Adverse Event assessment			X	X	X	X	X
Phone follow-up					X		X

a. As a 14-day waiting period must occur between each subject before the next subject can be enrolled and dosed, the subject is allowed to sign the consent form 45-60 days prior to study treatment.
b. The assessments of Visit 2 will be performed within 28 days from Visit 1, the assessments of Visit 3, 4 will be performed within 7 (+7**)** calendar days after Visit 2,3 respectively. The assessment of Visit 5 will be performed 7 (-2) or 7 (+5) calendar days after last dose of study drug. The assessment of Follow-up visit will be performed 4 weeks (±7 calendar days) after last dose of the study drug.
c. Safety labs may be obtained up to 5 calendar days prior to treatment day of Visit 3, 4 at Penn State Health system.
d. Buffy coat will be isolated from whole blood for DNA extraction.
e. Subjects will fast from at least 2 hours before and one hour after taking the AGN-CognI.Q dose in Visit 2, 3 ,4.
f. A remote safety follow-up by phone on any AEs any time between Visit 2 and Visit 3, Visit 3 and Visit 4, Visit 4 and Visit 5.