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# CUSTIRSEN SODIUM

*Clusterin-Targeting Antisense Therapy*
*Oncolytic*

Rec INNM; USAN

AS TRPM2 ODN
ISIS-112989
OGX-011

Antisense oligonucleotide targeting fragment 186-206nt (coding sequence) of the human clusterin (*CLU*) gene

d(*P*-Thio)[[2'-*O*-(2-methoxyethyl)]m5rC-[2'-*O*-(2-methoxyethyl)]rA-[2'-*O*-(2-methoxyethyl)]rG-[2'-*O*-(2-methoxyethyl)]m5rC-A-G-C-A-G-A-G-T-C-T-T-C-A-[2'-*O*-(2-methoxyethyl)]m5rU-[2'-*O*-(2-methoxyethyl)]m5rC-[2'-*O*-(2-methoxyethyl)]rA-[2'-*O*-(2-methoxyethyl)]m5rU]DNA eicosasodium salt

2'-*O*-(2-Methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridine eicosasodium salt

CAS: 685922-56-9
CAS: 903916-27-8 (free acid)
EN: 311583

**ABSTRACT**

*Clusterin is a stress-induced cytoprotective chaperone protein that functions similarly to a small heat shock protein. Clusterin is expressed in a variety of cancers and associated with broad-spectrum treatment resistance. Custirsen sodium (OGX-011, ISIS-112989) is a 2'-methoxyethyl-modified phosphorothioate antisense oligonucleotide (ASO) that is complementary to clusterin mRNA. In preclinical cancer models custirsen potently inhibited clusterin expression and increased sensitivity to a variety of treatments, including hormone therapy, radiation therapy and chemotherapy. Custirsen has been shown to be well tolerated in early clinical trials, with demonstrated clinical biological activity in human malignant and nonmalignant tissues. Randomized phase III trials of custirsen in combination with chemotherapy are planned in patients with castration-resistant prostate cancer.*

**BACKGROUND**

The development of treatment resistance is a common feature of solid tumor malignancies. A number of mechanisms have been identified that contribute to therapeutic resistance and cancer progression, including increased expression of prosurvival or antiapoptotic genes (1) such as those transcriptionally controlled by heat shock factor protein 1 (HSF 1) (2). HSF 1 is the key regulator of the heat shock response, a highly conserved protective mechanism for eukaryotic cells under stress, and has been associated with oncogenic transformation, proliferation and survival (2). Therefore, targeting HSF 1-associated pathways implicated in cancer progression and treatment resistance is a rational therapeutic strategy.

Clusterin (also known as testosterone repressed prostate message 2, apolipoprotein J or complement cytolysis inhibitor, among others) is one such HSF 1-regulated protein of potential therapeutic importance. The clusterin gene (*CLU*) on chromosome 8p21-p12 has been linked to numerous physiological and pathological processes due to the binding of the clusterin protein with a wide variety of client proteins (3). The amino acid sequence of clusterin is highly conserved across species; in humans, clusterin exists as both an intracellular truncated 55-kDa nuclear form and a 75-80-kDa heterodimeric secreted glycoprotein (4). Clusterin has been described as being both proapoptotic (5, 6) and antiapoptotic (7, 8). The secreted form of clusterin has been shown to be cytoprotective and antiapoptotic, whereas the nuclear form is proapoptotic (9, 10). There are two transcriptional isoforms of human *CLU* (isoform 1, NM_001831 [GenBank]; isoform 2, NM_203339 [GenBank]). These isoforms result from different transcriptional initiation sites, are only produced in humans and chimpanzees and result in proteins that have different

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*N*-termini. Both *CLU* isoforms produce proteins that are cytoprotective, although isoform 1 is capable of producing a splice variant that allows the protein to be transported into the nucleus using a nuclear localization sequence, resulting in the nuclear, proapoptotic form of clusterin (10).

Clusterin is expressed in a variety of human cancers, including those of the breast, lung, bladder, kidney, colon–rectum and prostate (11-16). In cancer, clusterin has been largely defined as functioning to inhibit apoptosis. It is activated after therapeutic stress (17-20), acting as a cytoprotective chaperone, much like an ATP-independent small heat shock protein, and its transcription is promoted by HSF 1 (4, 21). Clusterin's ability to inhibit apoptosis has also been shown to involve inhibition of activated BAX, a proapoptotic Bcl-2 family member (22), and activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway through the megalin cell-surface receptor (5). In xenograft models, clusterin expression increases in response to cell stress induced by a variety of factors, including standard treatment for cancer (19, 20, 23, 24). Forced overexpression of clusterin in cancer models confers resistance to radiation, hormone therapy and chemotherapy, whereas inhibition of clusterin expression enhances apoptotic death from these treatment modalities (17, 19, 20).

Antisense oligonucleotide (ASO) therapy is one strategy to specifically target functionally relevant genes. ASOs are chemically modified stretches of single-strand DNA complementary to mRNA regions of a target gene that inhibit translation by forming RNA/DNA duplexes, thereby reducing mRNA and protein levels of the target gene (25). The specificity and efficacy of an ASO relies on the precise targeting afforded by strand hybridization, where only a perfect match between the target mRNA sequence and the ASO will lead to hybridization and inhibition of translation. Phosphorothioate ASOs are water-soluble, stable agents resistant to nuclease digestion through substitution of a nonbridging phosphoryl oxygen of DNA with sulfur (26).

In clinical trials, continuous or frequent i.v. infusions were required to administer the first generation of phosphorothioate ASOs because of their short tissue half-life, a major technical limitation. Therefore, effort has been made to improve the stability and efficacy of ASOs by modifications of the phosphodiester linkage, the heterocycle or the sugar. One such alteration is the 2′-*O*-(2-methoxy)ethyl (2′-MOE) modification to the 2′-position of the carbohydrate moiety. 2′-MOE ASOs form duplexes with RNA with a significantly higher affinity relative to unmodified phosphorothioate ASOs. This increased affinity has been shown to result in improved antisense potency in vitro and in vivo. In addition, 2′-MOE ASOs display significantly improved resistance against nuclease-mediated metabolism relative to first-generation phosphorothioate ASOs, resulting in an improved tissue half-life in vivo, which results in a longer duration of action and allows for a more relaxed dosing regimen (27). Finally, these second-generation phosphorothioate ASOs have the potential for a more attractive safety profile relative to unmodified phosphorothioate ASOs (28).

Custirsen sodium is a 21-nucleoside ASO complementary to the clusterin mRNA AUG translation initiation site. The custirsen sequence was identified as the most potent to inhibit *CLU* expression after the gene was "walked" with a series of antisense sequences. Custirsen is a second-generation phosphorothioate and incorporates the 2′-MOE modification with 4 2′-MOE-modified nucleosides at the 3′ side, 4 2′-MOE-modified nucleosides at the 5′ side and 13 2′-deoxyribonucleosides in between (referred to as a 4-13-4 MOE gapmer).

## PRECLINICAL PHARMACOLOGY

Custirsen is a potent inhibitor of clusterin expression in vitro and in vivo (27). Furthermore, custirsen only inhibits the expression of the antiapoptotic secreted form of clusterin, with no effect on the proapoptotic nuclear form of clusterin (29). Unmodified phosphorothioate ASOs have relatively short serum and tissue half-lives (< 2 and 4 h, respectively) and only small amounts of full-length ASO can be detected in tissues after 24 h. By contrast, intermittent dosing of custirsen was as biologically effective as continuous dosing of an unmodified phosphorothioate with the same sequence (27). In preclinical efficacy studies, custirsen was shown to significantly enhance the therapeutic effect of hormone therapy, chemotherapy and radiation therapy in a variety of tumor models, including prostate, breast, non-small cell lung, bladder and kidney tumors (30).

## PHARMACOKINETICS AND METABOLISM

ASO metabolism is through degradation by endogenous plasma and intracellular nucleases, which are inhibited by the phosphorothioate backbone and 2′-MOE modifications (27). In general, ASOs are rapidly cleared from plasma as a result of wide distribution into tissues, except for the brain, as they do not cross the blood–brain barrier. After systemic administration, the highest ASO tissue concentrations can be found in the kidney, liver, spleen and lymph nodes.

In mouse and primate studies (31), custirsen was rapidly cleared from plasma in both species. Plasma concentrations of custirsen generally peaked at the end of the infusion period and then decreased in an apparently biexponential fashion, which included two distinct half-lives. The half-life values associated with the distribution phase ranged from 0.47 to 1.02 h in the monkey. The apparent terminal elimination half-life was much slower (37.5 and 137.9 h, respectively, in mice and monkeys) than the distribution phase and is thought to reflect a composite of the slow rates of elimination of drug from the various tissues. There was no suggestion of plasma accumulation or changes in plasma kinetics after multiple dosing. The plasma concentration–time profiles were dose-dependent, showing increased plasma concentrations in monkeys with increasing dose over the entire dose range evaluated (1-10 mg/kg/week). Plasma AUC values appeared to increase dose-dependently but somewhat more than dose-proportionally over the entire dose range evaluated in monkeys. Hence, mean monkey plasma clearance values appeared to exhibit an inverse dose-dependency over the evaluated dose range. The maximum concentration in monkeys increased proportionally with increasing doses. Following systemic administration, custirsen was broadly distributed and found in most mouse and monkey tissues; mean concentrations of custirsen increased with dose in all tissues examined except brain. Approximately 90% of the oligonucleotide in tissues was the intact, full-length custirsen oligonucleotide. The highest concentrations of custirsen were found in kidney, spleen and liver, with generally lower levels noted in reproductive organs such as the prostate, testes, ovaries and uterus. Drug concentrations in male monkey prostate tissue were detected following the lowest dose administered (1 mg/kg) and increased in a

dose-dependent manner, with average concentrations in prostate exceeding 8 µg/g tissue (approximately 1 µM) at a dose of 10 mg/kg, which well exceed in vitro concentrations associated with a biological effect.

In humans, plasma pharmacokinetic parameters for custirsen were as predicted from the preclinical studies. In the first-in-human study with custirsen, mean plasma distribution half-life ranged from 0.476 to 3.83 h, with a trend for longer values with higher doses. Average peak concentrations and AUC were dose-dependent and displayed proportional and predictable increases in a linear fashion. Mean maximum plasma concentration at 640 mg was 61.1 µg/mL (95% confidence interval [CI]: 55.3-66.9) after the day 1 infusion and 69.9 µg/mL (95% CI: 64.8-74.9) after the day 29 infusion. Clearance was similar across all subjects and occasions. Overall, there was no sign of plasma accumulation from repeated dosing (32). Similar pharmacokinetic parameters were observed when custirsen was combined with docetaxel on either a weekly or every-3-week schedule, or with gemcitabine/cisplatin chemotherapy (33, 34).

Prolonged custirsen tissue concentrations associated with biological effect have also been attained in humans (32). The first-in-human phase I study with custirsen used a neoadjuvant design with weekly dosing of custirsen followed by prostatectomy. This permitted an assessment of the prostate and lymph node specimens for tissue levels of custirsen. At doses of 320 mg and higher, concentrations of full-length custirsen were achieved that have been associated with a preclinical effect, and a biological effect was observed, with dose-dependent inhibition of clusterin expression in prostate cancer cells. There were dose-proportional increases in custirsen tissue concentrations and no apparent effect of timing of surgery (performed within 7 days of the last dosing) on custirsen tissue concentrations. Mean tissue concentrations at doses of 320, 480 and 640 mg were 1.67 (95% CI: 1.07-2.26), 2.29 (95% CI: 1.31-3.27) and 4.82 (95% CI: 3.54-6.10) µg/g of prostate tissue, respectively, corresponding roughly to concentrations of 223, 306 and 644 nM, respectively.

## SAFETY

In preclinical toxicity studies there were no signs of toxicity observed at doses up to 50 mg/kg in mice or up to 10 mg/kg in monkeys (31). The primary toxicities were alterations in liver function in the form of elevated transaminases in mice at a dose of 50 mg/kg, immune stimulation in the form of lymphohistiocytic cell infiltrates in mice, and minor evidence of complement activation related to peak concentration in monkeys at 10 mg/kg.

In the first-in-human study (32), dose-limiting toxicity was not observed at any of the dose levels evaluated and adverse events were limited to grade 1 or 2 only. Toxicity appeared to be dose-related and tended to occur within the first week and diminish with continued dosing. Grade 1 leukopenia and thrombocytopenia were observed, with thrombocytopenia increasing in frequency with higher doses ($P = 0.04$), with three of six patients experiencing grade 1 thrombocytopenia and two of six experiencing grade 1 leukopenia at 640 mg. Grade 1 anemia was seen in 19 of the 25 patients but did not appear to be dose-dependent ($P = 0.44$). The most common nonhematological adverse events were fever, fatigue and rigors, which usually occurred several hours after completion of the infusion and were self-limiting. Fever and rigors appeared to be dose-related ($P = 0.001$ and $P < 0.0001$, respectively), with five of six patients at the dose of 640 mg experiencing fatigue and fever, and all six patients experiencing rigors at this dose. The fever and rigors typically occurred on day 1 and 3 infusions, lessened after the day 5 infusion and did not occur with the day 8 and subsequent infusions. Grade 1 and 2 elevations in hepatic transaminases were also observed. At the dose of 640 mg, four of six subjects had increases in AST and ALT, with two of the six subjects experiencing grade 2 AST and/or ALT elevation. Elevated hepatic transaminases were observed to occur by day 8, but resolved to grade 1 or less by day 15-22 despite continuation of custirsen therapy. There was no apparent dose-dependent induction of serum complement C3a.

With custirsen in combination with chemotherapy, there does not appear to be a clinically significant worsening of chemotherapy-related side effects. Standard doses of docetaxel (33) or gemcitabine and cisplatin (34) could be safely delivered with biologically active doses of custirsen. In a randomized study of combination of docetaxel and custirsen versus docetaxel alone (35), there was no increase in the occurrence of grade 3 or 4 or serious adverse events. Toxicities that were more common on the combination treatment included the typical acute side effects with custirsen seen in prior studies (fever, rigors, sweating), as well as neuropathy, limb edema and lymphopenia.

## CLINICAL STUDIES

To date, 294 patients have been treated with custirsen in 6 phase I and II clinical trials. The first-in-human phase I study was a neoadjuvant trial with custirsen given prior to radical prostatectomy in 25 men with localized prostate cancer (32). A phase I trial of docetaxel and custirsen accrued 40 patients with a pathological diagnoses of cancers that had been reported in the literature to express clusterin (33). A phase I/II trial accrued 85 patients with non-small cell lung cancer to combination treatment with custirsen and gemcitabine/cisplatin chemotherapy (34). Two phase II trials of docetaxel and custirsen combination therapy have been conducted: a trial in patients with metastatic breast cancer that enrolled 15 patients (36) and a randomized trial in patients with castration-resistant prostate cancer who were chemotherapy-naïve accrued 81 patients in total (35). Finally, a randomized phase II trial evaluated the combination of mitoxantrone or docetaxel with custirsen in patients with castration-resistant prostate cancer that had progressed after prior docetaxel chemotherapy (37).

The first-in-human phase I study with custirsen used a novel neoadjuvant design to identify effective biological dosing of custirsen to inhibit clusterin expression in human cancer (32). Twenty-five male patients with localized prostate carcinoma and high-risk features were treated with custirsen given as a 2-h i.v. infusion prior to radical prostatectomy within 7 days of the last custirsen dose. This was a dose-escalation study in which doses of 40 (one patient), 80 (three patients), 160 (three patients), 320 (six patients), 480 (six patients) or 640 mg (six patients) were given as 2-h i.v. infusions on days 1, 3, 5, 8, 15, 22 and 29 for one cycle only. Neoadjuvant hormone therapy consisting of buserelin acetate and flutamide was administered concurrently. Prostatectomy specimens were then used to evaluate clusterin expression for both inter- and intrapatient comparisons to baseline. In this way, changes in expression of clusterin could be correlated to the dose of drug received and drug levels within the

prostate tissue itself could be determined. In this study, treatment was well tolerated and custirsen produced statistically significant, dose-dependent effects on suppression of clusterin expression in normal and tumor tissue. With this design and the use of these pharmacokinetic and pharmacodynamic endpoints, an effective biological dose of 640 mg was established based on the ability of custirsen to suppress clusterin mRNA by > 90% in prostate cancer tissue. Furthermore, in the historical control specimens treated with and without neoadjuvant hormone therapy, the mean apoptotic indices were 9.0% (95% CI: 5.1-13.0%) and 7.0% (95% CI: 4.2-9.9%), respectively. The apoptotic index from patients treated at the lower two dose levels of custirsen was 7.1% (95% CI: 2.4-11.8%), but at the 640-mg dose level the mean apoptotic index was 21.2% (95% CI: 18.1-24.2%). This is especially encouraging given the dose–response effect and the observation that prostate tissue had relatively lower concentrations of custirsen after systemic administration compared to other tissues in preclinical studies. Clusterin was also detectable in serum. In subsequent phase I and II studies with custirsen, a consistent decrease in serum clusterin was observed at 640 mg (33). Thus, clinical data clearly indicate that custirsen is biologically active in humans at doses of 640 mg and less.

In the phase I docetaxel/custirsen combination study, 32 patients were evaluable for response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Two patients, both with hormone-refractory prostate cancer and chemotherapy-naïve, had a confirmed partial response. Eleven patients had stable disease as best response (median duration: 6.5 months; range: 1.5-26.4 months). One of these patients had ovarian cancer (previously treated with paclitaxel and carboplatin) and subsequently achieved a complete response in measurable disease while on follow-up without further therapy, remaining in complete remission 4 years after completing protocol therapy. Fourteen patients with hormone-refractory prostate cancer were evaluable for post-treatment prostate-specific antigen (PSA) declines, with 3 patients having had prior chemotherapy with mitoxantrone or docetaxel. Six patients had a confirmed PSA response (defined as a post-treatment PSA decline of ≥ 50% from baseline, confirmed by a second value), one patient had an unconfirmed PSA response, and two patients had unconfirmed PSA decreases of 29% and 30% (33).

In the non-small cell lung cancer study (34), 12 confirmed partial responses were observed (objective response rate: 23%) and median progression-free survival was 101 days (range: 53-260+). Of the first 24 patients who had all been followed for 1 year, median survival was 383 days (19-751+), with 14 patients (58%) surviving for over 1 year. These overall survival data were considered clinically significant as compared to prior clinical trial data with chemotherapy alone.

The phase II trial of docetaxel and custirsen in patients with metastatic breast cancer initially evaluated 15 patients. Five partial responses were observed (objective response rate: 33%) but this just fell short of the a priori hypothesis for continuation to the second stage of the study (response rate ≥ 35%) (36). It is debatable whether the RECIST criteria response rate in a relatively small single-arm trial is a sensitive indicator of the clinical activity of an agent like custirsen that aims to improve chemosensitivity.

Because of the difficulty of interpreting antitumor responses of combination chemotherapy with a targeted agent, especially in patients with castration-resistant prostate cancer, a randomized phase II study was carried out in this population and updated results recently presented (38). Patients with chemotherapy-naïve, metastatic castration-resistant prostate cancer were randomized to receive either the docetaxel/custirsen combination or docetaxel alone as an internal control arm. Forty patients received combined therapy and 41 received standard docetaxel chemotherapy. The median cycles delivered for combined docetaxel/custirsen were nine cycles compared to only seven for docetaxel standard therapy. The PSA response rate (≥ 50% decline from baseline, confirmed by a subsequent value) was similar for both arms at approximately 50-60%. However, in the combination arm, there were no patients whose best PSA response was progression and 4% had objective disease progression as best response, while on the docetaxel standard therapy arm 7% of patients had PSA progression and 17% had objective disease progression as best response. Median progression-free survival was reported at 7.3 months (95% CI: 5.3-8.8) and 6.1 months (95% CI: 3.7-8.6), respectively, for the combination docetaxel/custirsen and standard therapy arms. Overall survival for patients in the docetaxel/custirsen arm was a median of 23.8 months (95% CI: 16.2-∞) and for those receiving standard docetaxel therapy the median overall survival was 16.9 months (95% CI: 12.8-25.8). In a preplanned multivariate analysis, baseline patient factors associated with improved overall survival were an ECOG performance status of 0 (hazard ratio [HR]: 0.28; $P < 0.0001$) and treatment assignment to the docetaxel/custirsen treatment arm (HR: 0.49; $P = 0.012$). The presence of metastases other than in bone or lymph node was associated with worse survival (HR: 2.13; $P = 0.01$).

A further trial in patients with castration-resistant prostate cancer was recently completed and initial results also presented (37). In this study, patients were included only if they had previously progressed on docetaxel within 6 months of study entry and were randomized to receive either docetaxel or mitoxantrone combined with custirsen in order to evaluate the hypothesis that custirsen could reverse docetaxel resistance or improve mitoxantrone efficacy in a chemotherapy-resistant population. Forty-two patients received at least 1 cycle of combined therapy with a median number of cycles delivered for the docetaxel/custirsen group being 7.5 and for the mitoxantrone/custirsen group 6.0. PSA declines of ≥ 90%, ≥ 50% and ≥ 30%, respectively, were seen in 20%, 40% and 55% of patients receiving docetaxel/custirsen and 0%, 27% and 32% of patients receiving mitoxantrone/custirsen. Pain responses were also seen in 67% and 50% of patients, respectively, receiving docetaxel/custirsen and mitoxantrone/custirsen. At a median follow-up of 13.3 months, 60% of patients were still alive in both arms. These results are of interest considering the docetaxel-resistant state of their disease, with the reported median survival for such patients being in the range of 1 year or less and PSA response rates on the order of 20% or less for patients receiving second-line chemotherapy (39).

Randomized phase III trials of custirsen in combination with docetaxel are now being planned.

## SOURCES

OncoGenex Pharmaceuticals (CA); discovered and optimized in collaboration with Isis Pharmaceuticals (US).

## DISCLOSURE

K.N. Chi has no disclosures. M.E. Gleave is a scientific founder and holds stock in OncoGenex Technologies.

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