



Isotechnika inc.

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**SCIENTIFIC MEETING
ABSTRACTS**

Updated December 2011

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A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 2 Trial of ISA247 in Patients with Chronic Plaque Psoriasis (J Am Acad Derm article)**Error! Bookmark not defined.**

The Novel Calcineurin Inhibitor ISA247: A More Potent Immunosuppressant Than Cyclosporin In Vitro (Transpl Int. article)**Error! Bookmark not defined.**

Pharmacometrics of Voclosporin in a Phase 2B Renal Transplant Trial

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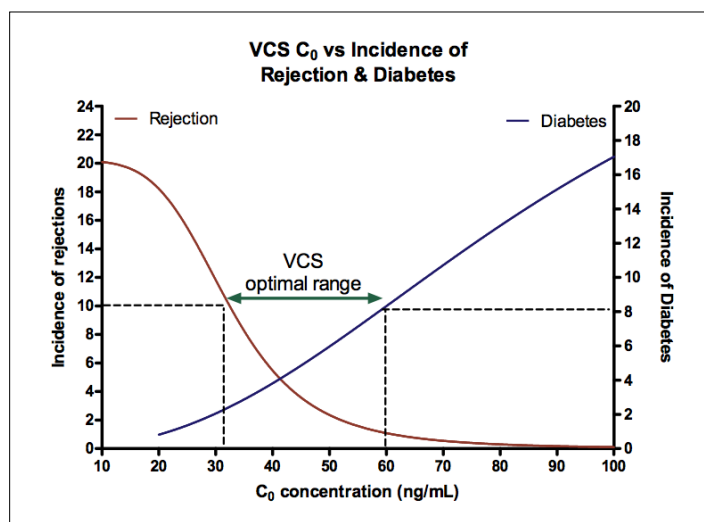
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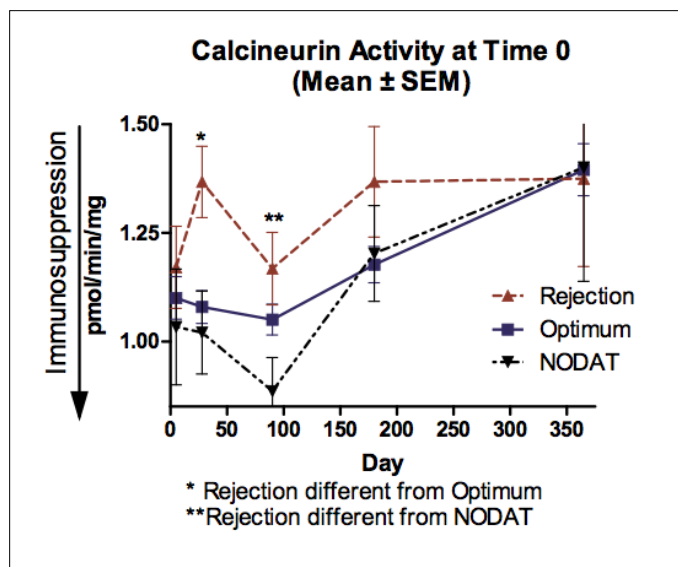
Purpose: Voclosporin (VCS) is a next generation calcineurin inhibitor (CNI) being developed for solid organ transplantation. Established therapeutic drug monitoring of CNI-based immunosuppression is based on trough concentration ranges that may not adequately determine clinical outcome. However, VCS has been developed using a pharmacometric approach which balances VCS concentration (PK), calcineurin inhibition (PD) and defined clinical outcomes—graft rejection (BPAR) and new onset diabetes (NODAT)—to determine an ideal therapeutic window.

Methods: PROMISE was a 12 month, randomized, concentration-controlled study in *de novo* renal transplant patients comparing three oral voclosporin dosing groups (low, mid, and high dose) to tacrolimus. A total of 334 patients were enrolled in the Phase 2B study of which 248 were randomized to the VCS arms. VCS trough concentrations and calcineurin activity (CNa) were determined using an LC/MS based assay.

Results: PK/PD modelling of BPAR and NODAT versus trough concentration (C_0) of VCS predicted an optimal C_0 range of between 32-60 ng/mL.



In addition, Cox regression analyses of calcineurin activity (CNa) and BPAR suggested patients are 1.7 times more likely to reject if CNa_0 was above 1.3 pmol/min/mg.



Conclusion: VCS efficacy and toxicity can be characterized by a classic sigmoid relationship with blood concentration. Furthermore, CNa_0 -based dosing offers the potential to determine VCS activity at the molecular site of action. A pharmacometric approach has enabled the quantification of a therapeutic window, unique for a CNI, which allows an enhanced ability for optimized and individualized dosing. This novel dosing paradigm for VCS will be explored in upcoming Phase 3 studies.

ESOT; August 30 – September 2, 2009; Paris, France

Efficacy of Voclosporin (ISA247) for Psoriasis Treatment – Results from the ESSENCE study

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Introduction

Calcineurin inhibitors (CNI) remain one of the systemic therapies of choice for treatment of severe plaque psoriasis. Voclosporin (VCS) is a new, tight binding CNI. The tighter binding and novel chemical structure results in an improved pharmacokinetic and pharmacodynamic profile, as well as a decreased adverse event profile, compared to traditional CNI. ESSENCE is a 3–arm trial of VCS compared to placebo and cyclosporine (CsA) in moderate to severe plaque psoriasis patients. This study design with a placebo and an active comparator arm allow for proper assessment of benefit/risk ratio.

Methods

A total of 642 patients (Canada, Germany and Poland) were enrolled in the 60 week ESSENCE study. Subjects were randomized to one of 3 treatment groups in 3:1:1 ratio (VCS 0.4 mg/kg bid, placebo, CsA 1.5 mg/kg bid, respectively) for 12 weeks after which the placebo group was converted to 0.4 mg/kg bid. After 60 weeks, all patients were followed for an additional 12 weeks after discontinuation of treatment. Achieving “clear” or “almost clear” in the Static Physician’s Global Assessment (SPGA) score after 12 weeks was the primary efficacy endpoint. Secondary efficacy endpoints and Quality of Life assessments were also collected on all study subjects. Patients were also closely monitored for changes in renal function, hypertension and hyperlipidemia.

Results and Conclusions

The head-to-head design of ESSENCE: CsA and placebo control groups, provides a direct comparison of safety and efficacy. Presentation of the final unblinded efficacy data for the current study will take place at CDA’s 84th Annual Conference.

CDA 2009; July 1-5, 2009; Vancouver, BC

Voclosporin (ISA247) Pharmacokinetic-Pharmacodynamic (PK-PD) Profile – Results from ESSENCE study

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Introduction

Cyclosporine (CsA) is an efficacious agent in plaque psoriasis, but suffers from dose-limiting toxicities. Voclosporin (VCS) is a next generation calcineurin inhibitor with increased potency, an improved PK-PD relationship and a wider therapeutic window. Data from a previous Canadian phase 3 trial showed that 91% of the reduction in Psoriasis Area and Severity Index (PASI) scores could be attributed to the trough concentrations of VCS during the study. The Phase 3 ESSENCE study, which is both placebo and CsA controlled, has just completed.

Methods

A total of 642 patients (Canada, Germany and Poland) were enrolled in the 60 week ESSENCE study. Subjects were randomized to one of 3 treatment groups in 3:1:1 ratio (VCS 0.4 mg/kg bid, placebo, CsA 1.5 mg/kg bid, respectively) for 12 weeks after which the placebo group was converted to 0.4 mg/kg bid. After 60 weeks, all patients were followed for an additional 12 weeks after discontinuation of treatment. Achieving “clear” or “almost clear” in the Static Physician’s Global Assessment (SPGA) score after 12 weeks was the primary efficacy endpoint. A subset of patients also participated in a PK-PD study at weeks 4, 12 and 24 to determine various PK-PD parameters.

Results and Conclusions

Blinded interim results demonstrate an acceptable pharmacodynamic response using the calcineurin assay. Utilization of PK-PD information may allow for improved patient management. Presentation of the unblinded PK-PD data will take place at CDA’s 84th Annual Conference.

CDA 2009; July 1-5, 2009; Vancouver, BC

Made in Canada: Development of Voclosporin (ISA247) for the Treatment of Psoriasis

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Background

Calcineurin inhibitor (CNI) based therapies are effective in the treatment of plaque psoriasis. Cyclosporine (CsA), a first-generation CNI, is efficacious, but has dose-limiting adverse events. Using a pharmacodynamic measure (calcineurin inhibition) to more accurately evaluate efficacy, voclosporin (VCS) was developed by Isotechnika, a Canadian company, to provide a drug with similar efficacy to CsA, but improved PK-PD and safety profiles.

Drug Development Pathway

A Canadian Phase 3 study demonstrated that VCS was efficacious and that blood concentrations correlated strongly with mean percentage reduction in psoriasis area and severity index (PASI). In the phase 3 randomized, multicentre, double-blind ESSENCE study, the efficacy and safety of VCS was compared to placebo and an active comparator, cyclosporine. Comparison with the CNI cyclosporine provided a proper assessment of benefit/risk ratio. Safety, efficacy and PK-PD results from the ESSENCE trial are currently blinded, but will be available for CDA's 84th Annual Conference.

Conclusions

VCS has been assessed for the treatment of psoriasis during a Phase 2a trial, a Canadian Phase 3 trial, and a Canadian/European Phase 3 trial in which Canadian sites participated. Canadian dermatologists have played a primary role in the development of this drug, not only acting as Investigators and sitting on Steering Committees, but also acting as impartial adjudicators on Data Monitoring Committees. Voclosporin is an example of the lead role Canadian Dermatology can play in drug development from Phase 1-3.

CDA 2009; July 1-5, 2009; Vancouver, BC

Pharmacometrics of Voclosporin: Quantification of a Therapeutic Window in a Phase 2b Renal Transplant Trial

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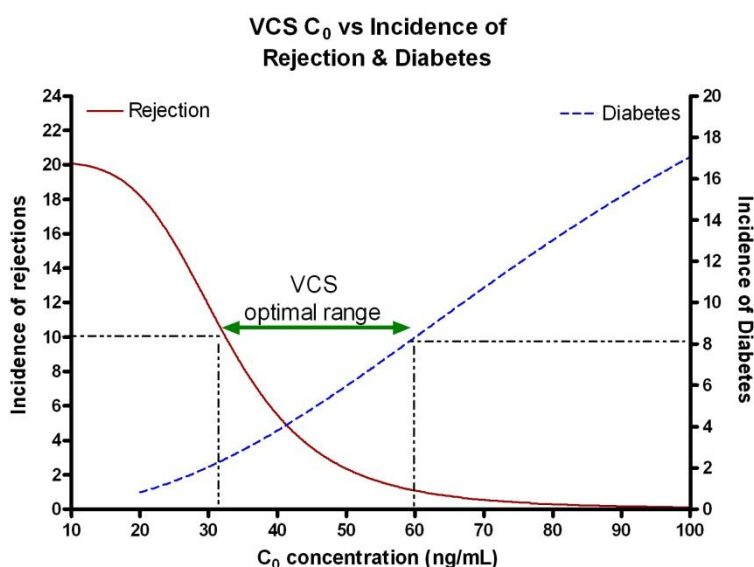
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Background:

Voclosporin (VCS) is a next generation calcineurin inhibitor being developed for solid organ transplantation. Traditionally, calcineurin inhibitor-based immunosuppression is titrated to trough concentration ranges chosen empirically to balance risk of over- and under-immunosuppression. VCS has been developed using a pharmacometric approach to predict the relationship between VCS concentration (PK), calcineurin inhibition (PD), and clinical outcomes. PK data from a recently completed Phase 2b renal transplant trial was modeled to quantify a therapeutic window for VCS using the clinical outcomes of rejection as a measure of under-immunosuppression and NODAT as a measure of dose related toxicity.

Methods:

VCS trough concentrations were determined using LC/MS in *de novo* renal allograft recipients (n = 248). Prediction of rejection and NODAT (using 2003 ADA criteria) was based on PK-PD modeling of the incidence of rejection and diabetes stratified by lowest and highest measured C₀ values, respectively. Rejections vs. C₀ were best fit to inhibitory effect sigmoid E_{max} model. NODAT vs. C₀ were best fit to a sigmoid E_{max} model.



The therapeutic window for VCS suggests a wide safety margin.

Conclusions:

VCS efficacy and toxicity can be characterized by classic sigmoid relationship with blood concentration. A pharmacometric approach has enabled the quantification of a therapeutic window, unique for a calcineurin inhibitor, which allows an enhanced ability for optimized and individualized dosing.

Pharmacometrics of Voclosporin: Predicting Clinical Outcome with Calcineurin Activity in a Phase 2b Renal Transplant Trial

Pat Mayo, PhD¹, Shamkant Mulgaonkar, MD², Anthony Jevnikar, MD³, A. Osama Gaber, MD⁴, Rita Alloway, PharmD⁵ and Herwig-Ulf Meier-Kriesche, MD⁶.

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Background:

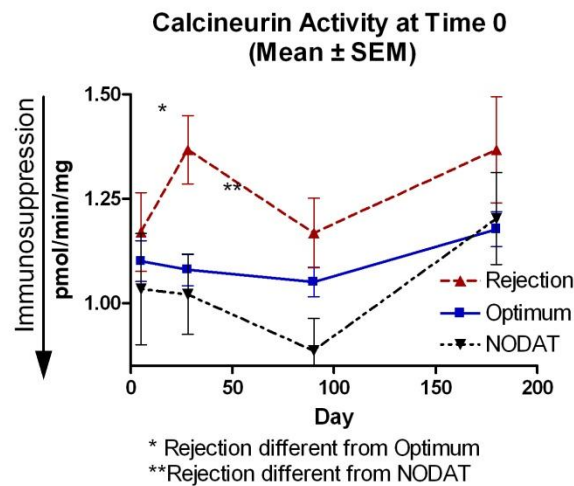
Voclosporin (VCS) is a next generation calcineurin inhibitor (CNI) being developed for solid organ transplantation. Traditional therapeutic drug monitoring of CNI-based immunosuppression is based on trough concentration ranges which may not adequately determine clinical outcome. VCS has been developed using an integrated pharmacometric approach in which pharmacokinetics (PK) and pharmacodynamics (ie, calcineurin activity, CNA) have been linked to the clinical outcomes of rejection and new onset diabetes after transplantation (NODAT).

Methods:

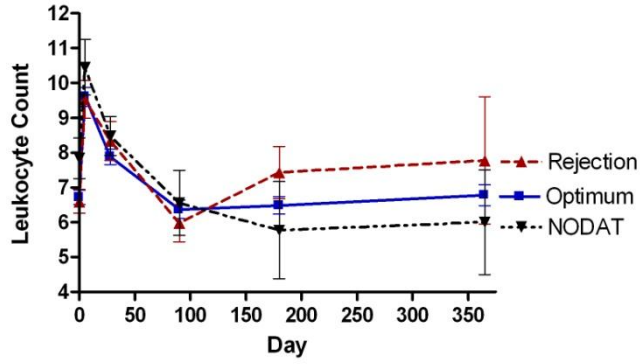
248 patients were randomized to three dose groups of voclosporin and similar doses of MMF. Time zero and two hour blood samples were obtained to measure PK and CNA using an LC/MS and P³²-based assay, respectively. PK and CNA were analyzed using linear regression, ANOVA and Cox regression. Outcomes were defined as optimum (patients without rejection or NODAT), rejection and NODAT. Leukocyte count was explored as a covariate to indicate general immunosuppression.

Results:

Overall the hazard ratio suggested patients are 1.7 times more likely to reject if calcineurin activity was above 1.3 pmol/min/mg. In addition a novel relationship was observed between CNA₀ and leukocyte count ($r = 0.55$, $p < 0.05$), which was also associated with clinical outcome. No relationship was observed between drug trough concentration and leukocyte count.



**Leukocyte Count by Day and Outcome
(Mean \pm SEM)**



Conclusions:

CNA –based dosing offers an opportunity to determine VCS activity at the site of action which can be directly linked to clinical outcome. This novel dosing paradigm for VCS will be explored in upcoming Phase 3 studies

ATC 2009; May 30 – June 3, 2009; Boston, MA

Modifiable Risk Factors for New Onset of Diabetes after Transplant: Data from the PROMISE Renal Transplant Trial

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Background: The leading causes of death in renal transplant patients include cardiovascular disease and infection—which have been linked to new onset diabetes mellitus after transplantation (NODAT). While calcineurin inhibitors (CNI's) are effective, they have common side effects: NODAT, hyperlipidemia and hypertension. Voclosporin is a novel CNI, developed using a pharmacodynamic approach, for use in autoimmune disease and solid organ transplantation.

Methods: PROMISE was a 6 month, randomized, concentration-controlled study in *de novo* renal transplants comparing three oral voclosporin dosing groups (low, mid, and high dose) to tacrolimus. Standardized criteria were used for determining the incidence of NODAT (2003 ADA), triglyceride and cholesterol levels (>2.8 mmol and 5.1 mmol respectively) and hypertension (treated with a medication for the reason of hypertension).

Results: 334 patients were enrolled. Baseline demographics were similar in all groups.

Randomization Group	NODAT	Triglycerides > Upper Limit of Normal	Total Cholesterol > Upper Limit of Normal	Hypertension (patients treated for an AE)
Tacrolimus (n=86)	16.4%	39.2%	7.6%	26.7%
Low dose voclosporin (n=84)	1.6%*	17.5%**	6.3%	32.1%
Mid dose voclosporin (n=77)	5.7%	29.7%	9.4%	22.1%
High dose voclosporin (n=87)	17.7%	27.5%	5.8%	24.1%

*p=0.031 vs. tacrolimus, **p=0.016 vs. tacrolimus

NODAT was statistically lower in the low dose voclosporin group and numerically lower in the mid dose group compared to tacrolimus. Fewer voclosporin-treated patients demonstrated hypertriglyceridemia while other lipid parameters were similar across treatment groups. There were no differences in treated hypertension.

Conclusion: Voclosporin offers similar efficacy to tacrolimus, with a reduced risk of NODAT, which may result in an improved cardiovascular risk profile.

Quebec Society of Nephrology; April 30 – May 2, 2009; Montebello, QC

Voclosporin (ISA247) Demonstrates a Reduced Risk of Metabolic Syndrome After Transplantation: Results From the Phase 2B PROMISE Trial

Zaltzman J¹, Campbell P², Cantarovich M³, Jevnikar A⁴, for the PROMISE Investigators

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Background: New onset diabetes mellitus (NODAT), hyperlipidemia and hypertension are common side-effects of calcineurin inhibitors (CNI's) and are established risks for Metabolic Syndrome. Voclosporin is a novel CNI, developed using a pharmacodynamic approach for use in autoimmune disease and solid organ transplantation. We hypothesize that voclosporin will demonstrate an improved incidence of NODAT compared to tacrolimus without an elevation in rates of hypertension and hyperlipidemia.

Methods: PROMISE was a 6 month, randomized, concentration-controlled study in *de novo* renal transplants comparing three oral voclosporin dosing groups (low, mid, and high dose) to tacrolimus. Incidence of NODAT was determined using the 2003 ADA criteria. The upper limit of normal for triglyceride and cholesterol levels were 2.8 mmol and 5.1 mmol, respectively.

Results: 334 patients were enrolled. Baseline demographics were similar in all groups.

Randomization Group	NODAT	Triglycerides > Upper Limit of Normal	Total Cholesterol > Upper Limit of Normal	Hypertension (patients treated for an AE)
Tacrolimus (n=86)	16.4%	39.2%	7.6%	26.7%
Low dose voclosporin (n=84)	1.6%*	17.5%**	6.3%	32.1%
Mid dose voclosporin (n=77)	5.7%	29.7%	9.4%	22.1%
High dose voclosporin (n=87)	17.7%	27.5%	5.8%	24.1%

*p=0.031 vs. tacrolimus, **p=0.016 vs. tacrolimus

NODAT was statistically lower in the low dose voclosporin, and numerically lower than tacrolimus in the mid dose group compared to tacrolimus. Fewer voclosporin-treated patients demonstrated hypertriglyceridemia. Other lipid parameters were similar across treatment groups.

Conclusion: Voclosporin may offer similar efficacy to tacrolimus with a reduced risk of metabolic syndrome symptoms, resulting in an improved cardiovascular risk profile.

CST 2009; March 4-8, 2009; Banff, AB

**The Pharmacokinetics and Pharmacodynamics (PK-PD) of Voclosporin (VCS) in Plaque Psoriasis:
A New Dosing Paradigm.**

Papp KA, Mayo PR, Langley RGB

The purpose of this study was to explore the PK-PD relationships of voclosporin (VCS) in patients with plaque psoriasis in order to develop an optimized dosing strategy. This study was part of a Phase 3, randomized, multicenter, double-blind, placebo-controlled study of VCS in plaque psoriasis patients.

Data of all dose groups were pooled and categorized by the primary outcome, PASI75 at 12-weeks. VCS concentration and calcineurin activity/inhibition were determined by validated LC/MS and p32-radionuclide assays, respectively. Concentration and calcineurin activity were correlated with PASI scores using simple E_{max} and inhibitory E_{max} models.

Of the total 451 patients, 138 patients participated in the PK-PD portion of the study. Concentration, calcineurin activity (CNa) and calcineurin inhibition (CNi), all at 2 hours post-dose, were stratified by the achievement of PASI75.

Table 1: VCS Concentration, CNa and CNi at Week 12, Stratified by Achievement of PASI75

PASI75	C2 (ng/mL)	CNa2 (pmol/min/mg)	CNi2 (%)
Yes	117.4 ± 57.6*	0.79 ± 0.35*	45.6 ± 18.3*
No	58.8 ± 52.7	1.31 ± 0.63	35.8 ±

*Different from No PASI75 Group, $p < 0.001$

At week 12, the data show that calcineurin inhibition strongly correlates with PASI score. Patients achieving a PASI75 were then stratified by calcineurin inhibition at 4 weeks above or below 45%.

Table 2: PASI75 and Week 4 2-Hour Calcineurin Inhibition $\geq 45\%$

PASI75 (Week 12)	CNi2 $\geq 45\%$ (Week 4)	PASI Baseline (Week 0)	12-Week PASI	%ΔPASI (Week 12)
Yes	Yes	16.7 ± 5.1	2.2 ± 1.7*	-87.6 ± 8.0*
No	No	16.8 ± 5.4	12.7 ± 6.7	-21.5 ± 36.9

*Different from No PASI75 Group, $p < 0.001$

Calcineurin inhibition $\geq 45\%$ after 4 weeks of treatment was associated with achievement of a PASI75 by week 12, while patients with 45% CNi were not. The strong PK-PD relationships exhibited by VCS support the use of a 2-hour calcineurin test to optimize patient outcomes. Dosing to achieve 2-hr CNi $\geq 45\%$ after 4 weeks of treatment is therefore recommended in order to ensure optimal response. Increasing the dose of voclosporin may benefit those patients with suboptimal voclosporin serum levels who have not achieved a 25% improvement in PASI by week 4.

Psoriasis from Gene to Clinic 2008; December 4-6, 2008; London, UK

Improved Incidence of New Onset Diabetes Mellitus in Patients Receiving Voclosporin versus Tacrolimus: Final results of the PROMISE trial.

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Background: Voclosporin (ISA247) is a next-generation calcineurin inhibitor (CNI). A Phase 2b study (PROMISE) in *de novo* renal transplant patients comparing voclosporin to tacrolimus was recently completed.

Methods: The PROMISE trial was a 6 month, randomized, multicenter, open-label, concentration-controlled study comparing three oral voclosporin dosing groups (low, mid, high dose) with initial dosing ranging from 0.4 to 0.8 mg/kg BID to tacrolimus. New Onset of Diabetes after Transplantation (NODAT) was defined by the 2003 ADA guidelines.

Results: 334 patients were enrolled. All groups were similar in baseline demographics, excepting that the tacrolimus treatment group had significantly higher proportion of living donor recipients compared to the high dose group (72.1 vs. 57.4%, p=0.043).

Randomization Group	NODAT	Triglycerides > Upper Limit of Normal	Total Cholesterol > Upper Limit of Normal	Nankivell GFR (mL/min)
Tacrolimus (n=86)	16.4%	39.2%	7.6%	69
Low dose voclosporin (n=84)	1.6%*	17.5%**	6.3%	71
Mid dose voclosporin (n=77)	5.7%	29.7%	9.4%	72
High dose voclosporin (n=87)	17.7%	27.5%	5.8%	68

All voclosporin groups were non-inferior to tacrolimus in efficacy (BPAR) at 6 months. NODAT was statistically lower in the low dose voclosporin compared to tacrolimus (p=0.031), with a similar trend noted in the mid dose group. Fewer voclosporin-treated patients demonstrated hypertriglyceridemia (p=0.016). Other lipid parameters were similar across treatment groups. Despite a doubling of concentration from the low to high voclosporin dosing group, renal function was similar in all 4 arms of the study.

Conclusion: Voclosporin may offer similar efficacy to tacrolimus with an improved cardiovascular risk profile (NODAT and triglycerides).

ASN 2008; November 4-9, 2008; Philadelphia, PA

Efficacy and impact on renal function of voclosporin (ISA247): The phase 2 ‘PROMISE’ trial in *de novo* renal transplant recipients

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Introduction: Voclosporin (VCS) is a next generation calcineurin inhibitor (CNI), developed using a pharmacodynamic approach for use in autoimmune disease and solid organ transplantation. A Phase 2b study (PROMISE) in *de novo* renal transplant patients comparing voclosporin to tacrolimus was recently completed.

Methods: PROMISE was a 6 month, randomized, multicenter, open-label, concentration-controlled study comparing three oral VCS treatment groups (low, mid, high dose) with initial dosing ranging from 0.4 to 0.8 mg/kg BID to tacrolimus. The primary outcome of the trial was non-inferiority in biopsy proven acute rejection (BPAR) at 6 months. Renal function was determined by iothalamate GFR (iGFR), serum creatinine, Nankivell, and Cockcroft-Gault equations.

Results: 334 patients were enrolled in the study. At 6 months, the primary efficacy objective of non-inferiority in BPAR was achieved in all three VCS treatment groups. Renal function as measured by iGFR and Nankivell GFR was similar in all treatment groups. Serum creatinine and Cockcroft-Gault creatinine clearance were statistically different in the VCS high dose group compared to tacrolimus.

Randomization Group	BPAR	iothalamate GFR (mL/min)	Serum Creatinine (µmol/L)	Nankivell GFR (mL/min)	Cockcroft-Gault CrCl (mL/min)
Low dose VCS (n=84)	10.7%	56±25	122±29	71±13	74±21
Mid dose VCS (n=77)	9.1%	64±38	123±22	72±12	79±20
High dose VCS (n=87)	2.3%	60±48	131±30*	68±13	71±23†
Tacrolimus (n=86)	5.8%	65±44	120±26	69±29	79±22

* $p=0.005$ vs. tacrolimus, † $p=0.023$ vs. tacrolimus

Discussion: This study demonstrates that VCS is effective, and renal function overall is excellent in all groups. Reduced renal function (SCr, Cockcroft-Gault) noted in the high dose group is within a clinically acceptable range. These findings suggest a wide window for VCS dosing compared to CNI's currently used in transplantation.

Conclusion: VCS represents a next generation CNI with a wide therapeutic window which may allow for easier dosing.

ISN Nexus symposium Tx and the Kidney 2008; September 25-29, 2008; Rome, Italy

Voclosporin (ISA247): The Phase 2 ‘PROMISE’ *de novo* Renal Transplant Trial Demonstrates Efficacy And An Improved Safety Profile Across A Wide Therapeutic Range.

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Background: Voclosporin (VCS) is a next generation calcineurin inhibitor (CNI), developed using a pharmacodynamic approach for use in autoimmune disease and solid organ transplantation. Voclosporin was previously shown to be efficacious and well tolerated in stable renal transplant recipients when compared to cyclosporine. A Phase 2b study (PROMISE) in *de novo* renal transplant patients comparing voclosporin to tacrolimus was recently completed.

Methods: PROMISE was a 6 month, randomized, multicenter, open-label, concentration-controlled study comparing three oral voclosporin dosing groups (low, mid, high dose) with initial dosing ranging from 0.4 to 0.8 mg/kg BID to tacrolimus. *De novo* renal transplant recipients received induction therapy with an IL-2r antibody, and maintenance treatment with mycophenolate mofetil and steroids. Voclosporin and tacrolimus doses were titrated to target trough concentrations. The primary efficacy parameter of the trial was non-inferiority (in at least one dose group) in biopsy proven acute rejection (BPAR) at 6 months as compared to tacrolimus. Secondary objectives included: proportion of patients with new onset of diabetes after transplant (NODAT), hyperlipidemia, and hypertension; laboratory parameters; renal function; PK/PD relationships; patient and graft survival. NODAT was defined by the 2003 ADA guidelines.

Results: 334 patients were enrolled and key results are listed below:

Randomization Group	BPAR	Patient/Graft Survival	Nankivell GFR (mL/min)	NODAT
Tacrolimus (n=86)	5.8%	97.6%	69	16.4%
Low dose VCS (n=84)	10.7%	100%	71	1.6%*
Mid dose VCS (n=77)	9.1%	100%	72	5.7%
High dose VCS (n=87)	2.3%	98.8%	68	17.7%

**p*=0.031 vs. tacrolimus

At 6 months, the primary efficacy objective of non-inferiority in BPAR was achieved in all three voclosporin treatment groups. In all groups, patient and graft survival were excellent. The incidence of NODAT in the low dose voclosporin group was significantly lower than the tacrolimus group, and was numerically lower in the mid dose group. Despite a doubling of concentration from the low to high dosing group renal function was similar in all 4 arms of the study.

Conclusion: This large dose finding phase 2b study demonstrated that BPAR was non-inferior to tacrolimus in all voclosporin treatment groups. While efficacy appeared to be dose dependent and numerically better in the highest dose voclosporin group, the safety profile was similar or better in all voclosporin groups compared to tacrolimus. Kidney function was also excellent in all treatment groups. These results support the continuing clinical development of voclosporin.

TTS 2008; August 10-14, 2008; Sydney, Australia

Using Voclosporin Pharmacokinetics (Concentration) and Pharmacodynamics (Calcineurin Activity) to Predict Optimum Immunosuppression in a Phase 2b Renal Transplantation Trial

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Background: Voclosporin (VCS), a next generation calcineurin inhibitor, developed for solid organ transplantation. Traditionally, calcineurin inhibitor-based immunosuppression is titrated to trough concentration ranges (C₀). VCS has been developed using calcineurin activity (CNA) as a biomarker of immunosuppressant activity. Data just became available from a Phase 2b renal transplant trial to explore the PK and PD of VCS as a means of dose optimization.

Methods: A subset of *de novo* renal allograft recipients (n = 99) divided into three dose groups participated in a sparse sampling PK-PD protocol which measured VCS concentrations and CNA at time 0, 1, 2, and 4 hours. Drug concentrations were determined using LC/MS. CNA was determined with a P32-based assay. Both PK and PD were analyzed using standard non-compartmental analysis, t-test, and receiver-operator characteristic analysis. Data up to and including 180 days were stratified by clinical outcomes defined as optimum and as rejection.

Results:

Variable	Outcome	Mean ± sd	p	ROC	P
C ₀	Optimum	43.3 ± 26.7	0.013	0.617	0.040
	Rejection	33.4 ± 16.8			
AUC(0-4)	Optimum	638.4 ± 398.4	0.356	0.584	0.146
	Rejection	564.2 ± 364.6			
CNA ₀	Optimum	1.03 ± 0.44	0.002	0.671	0.003
	Rejection	1.33 ± 0.56			
CNA _{min}	Optimum	0.40 ± 0.30	0.007	0.601	0.08
	Rejection	0.59 ± 0.51			

C₀ = Concentration at Time 0

AUC₍₀₋₄₎ = Area-Under-the-Curve from 0 to 4 hours

CNA₀ = Calcineurin Activity at Time 0

CNA_{min} = Minimum Measured Calcineurin Activity

CNA at time 0 was found to be superior to trough and AUC₍₀₋₄₎ as a predictor of clinical outcome. In addition, ROC analysis suggests that trough was also a useful predictor of clinical outcome. Maximum calcineurin inhibition in the optimum group compared to the rejection group was 61% and 55%, respectively when using time zero as baseline.

A discriminant analysis correctly identified 83.2% of patients as optimum without rejection based on a combination of trough concentration and CNA. Interestingly, the use of post-dose time points for concentration did not improve predictive performance. PK-PD correlation between drug concentration and CNA revealed a good relationship with an E_{max} of 1.5 ± 0.03 pmol/min/mg and an EC₅₀ of 97.5 ± 5.4 ng/mL.

Conclusions: PD based dose optimization using the direct measurement of CNA may provide a more accurate means of dose titration than traditional PK methods. PK factors with known variability in *de novo* transplant patients such as polymorphisms in drug metabolism (CYP450) and transport (p-glycoprotein) are summarized by direct measurement of the drugs molecular target. This novel PD dosing paradigm for VCS will be explored more in detail in upcoming Phase 3 studies.

TTS 2008; August 10-14, 2008; Sydney, Australia

Continued Efficacy and Safety With ISA247 as Determined by Body Surface Area Assessment After 60 Weeks of Systemic Treatment of Plaque Psoriasis

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Introduction

ISA247, a next generation calcineurin inhibitor (CNI), has demonstrated increased potency and decreased toxicity compared to other CNi's. A 60 week Phase III study with ISA247 in moderate to severe plaque psoriasis has been completed.

Methods

Patients (n=451) were randomized to placebo (12 weeks), 0.2, 0.3, or 0.4 mg/kg bid ISA247 for 24 weeks. At 12 weeks, the placebo group was switched to 0.3 mg/kg bid. During the trial extension, from weeks 25 to 60, patients (n=296) continued to receive 0.3 mg/kg bid ISA247. The primary endpoint of the study was a 75% reduction in PASI score (PASI 75) at week 12. Body Surface Area (BSA) was also measured and a 70% reduction of the BSA (BSA70) was calculated.

Results

In the ITT population, PASI 75 was observed at 12 weeks in 4.0%, 16.3%, 25.2%, and 46.8% of those receiving placebo, 0.2, 0.3, and 0.4 mg/kg bid ISA247, respectively. Similarly, BSA70 was observed in 5.2%, 20.2%, 24.8%, and 47.5% of patients in the four study arms at 12 weeks and 41% of patients overall at 60 weeks. No differences in cholesterol, triglycerides, or other biochemical parameters were observed between treatment and placebo groups. Most adverse events were mild and evenly dispersed in treatment and placebo groups (headache, diarrhea, and hypertension). There was minimal change in renal function with a maximal mean increase in serum creatinine of 5.6 µmol/L at 24 weeks in the highest dose group. Only 4% of patients experienced clinically significant decrease in renal function at 60 weeks which returned to normal after discontinuation of treatment.

Conclusions

ISA247 is effective and well tolerated for the treatment of plaque psoriasis. Patients maintained a positive response throughout the 60 week study, indicated by PASI75 and BSA70 measurements. ISA247 appears to have similar efficacy and decreased toxicity when compared to cyclosporine literature.

CDA 2008; June 27 – July 2, 2008; Montreal, QC

Single and Multiple Evaluations of QTc Prolongation with ISA247, a novel calcineurin inhibitor: Where did the Single Dose Effect Go?

Objective

ISA247 is a novel calcineurin inhibitor developed for the prevention of organ graft rejection and the treatment of autoimmune diseases, such as psoriasis. The effect of ISA247 on cardiac repolarization was evaluated extensively in both single and multiple dose thorough QT/QTc Studies ("TQTS").

Method

Single dosing ranged from 0.5 to 4.5 mg/kg and multiple dosing ranged from 0.3 to 1.5 mg/kg BID. Both studies included placebo and moxifloxacin arms. Serial ECG and drug concentrations were obtained on Day 1 and after the morning dose on Day 7. Studies were in compliance with the ICH E14 guidance.

Results

The single dose TQTS demonstrated a maximal placebo-subtracted change of QTc from baseline (MP-SdQTc) in the 4.5mg/kg group of 34.6 msec. In contrast, the multiple dose TQTS finding was 2.8 msec MP-SdQTc in the 1.5mg/kg group (Upper 95% CI: 6.9 msec). No metabolite or electrolyte effect was seen.

Conclusion

The results of these studies are consistent, both internally, and in correlation between identical doses in the two studies. The QTc effect seen in the single dose study diminishes after steady state dosing. Drug exposure to steady state appears to pose little likelihood for emergence of arrhythmia.

DIA 2008; June 22-26, 2008; Boston, MA

ISA247: A Phase IIB Multicenter, Open Label, Concentration-Controlled Trial in *de novo* Renal Transplantation

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Background: ISA247 is a novel calcineurin inhibitor (CNI), developed using a pharmacodynamic approach for use in autoimmune disease and solid organ transplantation. In moderate to severe plaque psoriasis, a Canadian Phase III trial has demonstrated that ISA247 is efficacious with minimal changes to renal function and a European trial is presently underway comparing ISA247 to cyclosporine A (CsA). In renal transplantation, a Phase IIa study comparing ISA247 to CsA in stable renal transplant recipients demonstrated ISA247 to be efficacious and well tolerated. A Phase IIb study in *de novo* renal transplant patients comparing ISA247 to tacrolimus is on-going and final data will be available May 2008. We hypothesize that ISA247 is non-inferior to tacrolimus in terms of efficacy.

Methods: This is a 6 month, randomized, multicenter, open-label, concentration controlled study comparing three oral ISA247 dosing groups (0.4, 0.6, or 0.8 mg/kg bid) to tacrolimus in 42 North American transplant centres. All CNI's were titrated to target trough concentrations. Inclusion criteria included males and (non-pregnant) females between the ages of 18-65 who were receiving a first deceased or living donor renal transplant. Cold ischemia times were to be ≤ 24 hours, and peak panel reactive antibodies $\leq 30\%$. The primary efficacy parameter of the trial is non-inferiority (in at least one dose group) in biopsy proven acute rejection (BPAR) at 6 months as compared to tacrolimus. Secondary objectives include: renal function, PK/PD relationships; patient and graft survival; and proportion of patients with hypertension, hyperlipidemia or new onset diabetes mellitus (NODM).

Results: Interim data, as previously presented at the 2007 ATC, demonstrated that ISA247 had rejection rates similar to tacrolimus (ISA247 0.4 mg/kg bid 11%, ISA247 0.6 mg/kg bid 8%, ISA247 0.8 mg/kg bid 3%, tacrolimus 9%) and confirmed previous results indicating an improved safety profile. 334 patients have now been enrolled between January 2006 and June 2007, with an optional extension to 12 months added to the trial. A recent approval by both FDA and Health Canada has allowed continued use of ISA247 in these patients until commercialization. The six month final results will be available for presentation at ATC 2008.

ATC 2008; May 31 – June 4, 2008; Toronto, ON

DIA QT & Arrhythmia Workshop; June 22-26, 2008; Boston, MA

Using the PK-PD Relationships of ISA247 With Calcineurin Inhibition and Mycophenolic acid With IMPDH Inhibition, in a Phase 2b Renal Allograft Transplantation Trial to Predict Optimum Immunosuppression.

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Background: ISA247, a novel calcineurin inhibitor, is intended for use in solid organ transplantation and autoimmune disease. Data collection from a Phase 2b renal transplant trial, evaluating ISA247, was recently completed with final analysis to be available May 2008. In transplantation, optimum immunosuppression must balance the risk of rejection with the risk of over-immunosuppression. In this study the PK-PD relationships of ISA247 and calcineurin inhibition (CNI) combined with mycophenolic acid (MPA) and inositol-monophosphate dehydrogenase inhibition (IMPDH) were combined to determine whether they could be used to predict clinical outcome.

Methods: A sparse sampling PK-PD protocol was utilized to measure ISA247 and MPA concentrations, CNI, and IMPDH inhibition. Drug concentrations were determined using LC/MS. CNI was determined with a P³²-based calcineurin inhibition assay. IMPDH inhibition was measured by quantifying xanthosine 5 monophosphate production using LC/MS. ISA247-CNI and MPA-IMPDH data demonstrated classical enzyme-substrate pharmacokinetics. Pooled concentration-effect data were fit to an Emax model and then stratified by the clinical outcomes of rejection and infection.

Results: As analysis is ongoing, final data are not available. However, preliminary analysis suggests a pharmacodynamic combination index can be used to predict patient outcomes. This suggests a correlation between pharmacodynamics and clinical outcome. The index shows the presence of four distinct treatment groups. Patients without rejection and infection representing optimal immunosuppression, patients with rejection or infection representing inadequate or excessive immunosuppression, respectively, and a fourth group demonstrating both rejection and infection. The identification of this last group suggests a distinctly different pathophysiology. Overall, the analysis suggests that targeting certain pharmacodynamic ranges can optimize outcomes.

Conclusions: PK-PD relationships may provide a mechanism for dose optimization based on a total immunosuppressive index. PK-PD analysis may also demonstrate a group of patients at risk for rejection and infectious complications through a different etiology. Final data will be available for presentation in May 2008.

ATC 2008; May 31 – June 4, 2008; Toronto, ON

The ESSENCE Study: A Positive and Placebo Controlled, Double-Blind, Multicentre Study of ISA247 in Moderate to Severe Plaque Psoriasis

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Introduction: The International Conference on Harmonisation (ICH) E6 and E10 guidelines on clinical trial design state that trials should be designed with an adequate control group. Ciclosporin (CsA) is an efficacious agent in plaque psoriasis, but has dose-limiting toxicities. ISA247, a new calcineurin inhibitor, demonstrates increased potency with potentially less toxicity than CsA. A 60 week Canadian Phase III study in moderate to severe plaque psoriasis has been completed. A second Phase III study following the WMA policy is presently enrolling in the EU and Canada

Canadian Phase III Study Results: 451 patients were enrolled in this study in 4 dose groups: Placebo (12 weeks), 0.2, 0.3, and 0.4 mg/kg bid for 24 weeks. Placebo changed to 0.3 mg/kg bid at 12 weeks with all other groups changed to this dose at 24 weeks. Baseline SGA at entry was 3.2 ± 0.7 , and baseline PASI was 17 ± 6 . At 60 weeks, the percentage of patients with a 2-point reduction in SGA was 22%, and the PASI75 was 30%. Renal function remained stable throughout, and 4.4% of patients overall had a 30% decrease in calculated GFR. There were no differences in cholesterol, triglycerides, or other biochemical parameters. De novo hypertension (11%), nasopharyngitis (11%), URI (6%), and headache (4%), were the most common adverse events, and the majority of adverse events were mild in severity. After 12 weeks of follow-up, 79% of patients did not have a return of their disease and only 3.4% of patients overall experienced a psoriatic flare.

ESSENCE Study Design: Approximately 900 patients with stable moderate to severe psoriasis will be enrolled in this 24 week German/Polish/Canadian Phase III study in a 3:1:1 fashion: ISA247 0.4 mg/kg bid for 24 weeks, CsA 1.5 mg/kg bid for 24 weeks, or Placebo for 12 weeks. Patients on placebo will be converted to changed to ISA247 0.4 mg/kg bid at 12 weeks. Achieving "clear" or "almost clear" in the Static Physician's Global Assessment (SPGA) score after 12 weeks will be the primary efficacy endpoint. Secondary safety/adverse events endpoints include: renal function (confirmed $\geq 30\%$ rise in serum creatinine), hypertension (systolic ≥ 140 or diastolic ≥ 90 mmHg) and hypertriglyceridemia (fasting triglycerides ≥ 1.7 mmol/L). Secondary efficacy endpoints include: SPGA, PASI and Lattice System Physician's Global Assessment (LS-PGA). The Psoriasis Disability Index (PDI) and Dermatology Life Quality Index (DLQI) will be done to assess subject quality of life.

Conclusion: Most clinical studies of new immunosuppressant agents involve comparison to placebo only. The ESSENCE study design compares ISA247 against standardized dosing of CsA and against placebo in accordance with the ICH E6 and E10 guidelines so that a proper evaluation of the effectiveness and safety of each agent may be made. Enrollment has commenced in this study, and full data is expected in early 2008.

21st World Congress of Dermatology; October 1-5, 2007; Buenos Aires, Argentina

ISA247: Well-Tolerated After 60 Weeks of Continuous Therapy

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Introduction: Ciclosporin is an efficacious agent in plaque psoriasis, but its use is limited due to dose-limiting toxicities. ISA247, a new calcineurin inhibitor (CNI), demonstrates increased potency with potentially less toxicity than ciclosporin. A 60 week Phase III study with ISA247 in moderate to severe plaque psoriasis has been completed.

Methods: 451 patients were enrolled in a Canadian Phase III study in 4 dose groups: Placebo (12 weeks), 0.2, 0.3, and 0.4 mg/kg bid for 24 weeks. Placebo changed to 0.3 mg/kg bid at 12 weeks while all other groups changed to this dose at 24 weeks. 296 patients were enrolled into the extension study at 0.3 mg/kg bid for a total duration of 60 weeks of treatment.

Results: There was a statistically significant improvement in 2 point reduction in SGA and PASI75 response by 12 weeks in the groups treated with ISA247, and this efficacy continued throughout 60 weeks of treatment. At 60 weeks, the percentage of patients with a 2-point reduction in SGA was 29%, and the PASI75 was 31%. Adverse events noted in $\geq 3\%$ of all patients are listed below:

Adverse Events Occurring in $\geq 3\%$ of the Patients	ISA247 (N=296)
Hypertension	10.5%
Nasopharyngitis	10.5%
Upper respiratory tract infection	6.1%
Headache	4.1%
Arthralgia	3.4%
Influenza	3.4%
Nausea	3.0%

After study conclusion, 79% of patients did not have a return of their disease and only 3.4% of patients overall experienced a psoriatic flare during the twelve week follow-up.

Discussion: ISA247 is efficacious and well tolerated in plaque psoriasis. Adverse events were mostly mild in nature. The majority of patients treated with ISA247 did not suffer from a psoriatic flare and the majority of patients did not have a return of disease 12 weeks after discontinuing therapy. A European Phase III study (ESSENCE Study) comparing ISA247 to both ciclosporin and placebo in plaque psoriasis has commenced.

21st World Congress of Dermatology; October 1-5, 2007; Buenos Aires, Argentina

Long Term Safety of ISA247 in Plaque Psoriasis After 60 Weeks of Dosing

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Introduction

ISA247, a new calcineurin inhibitor (CNI), demonstrates comparable efficacy with less toxicity than cyclosporine. A 60 week Phase III study with ISA247 in moderate to severe plaque psoriasis has been completed.

Methods

Plaque psoriasis patients (n = 309) with $\geq 10\%$ BSA and PASI score of ≥ 10 were enrolled into a 24 week study followed by a 36 week extension study. Patients were initially randomized to either placebo (12 weeks), 0.2, 0.3, and 0.4 mg/kg bid of ISA247 for 24 weeks. Placebo patients changed to 0.3 mg/kg bid at 12 weeks with all other groups converted to this dose at 24 weeks. After a total of 60 weeks of treatment, patients were followed for an additional 12 weeks. The primary objective of this extension study is to investigate long-term safety and tolerability of ISA247.

Results

The four most common treatment-related adverse events included hypertension (10.8%), exacerbated hypertension (3.4%), nasopharyngitis (3.0%) and nausea (1.7%). Renal function (mean GFR) remained stable over the 60 weeks, with 4.5% of patients experiencing a 30% decline in renal function. Renal function returned to normal in these patients after discontinuation of drug. PASI 50 response remained stable (67%, 68%, 67% and 63%) at weeks 24, 36, 48, and 60.

Conclusions

Results of this 60 week study demonstrate that long-term use of ISA247 was generally safe, well tolerated, and efficacious in the treatment of patients with stable plaque psoriasis.

CDA 2007; June 29 – July 4, 2007; Toronto, ON

ISA247: Low Rates of Psoriatic Flare or Recurrence of Disease after Discontinuation of Therapy

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Introduction: Cyclosporine is an efficacious agent in plaque psoriasis, but its use is limited due to dose-limiting toxicities. ISA247, a new calcineurin inhibitor (CNI), demonstrates increased potency with potentially less toxicity than cyclosporine. A 60 week Phase III study with ISA247 in moderate to severe plaque psoriasis has been completed.

Methods: 451 patients were enrolled in a Canadian Phase III study in 4 dose groups: Placebo (12 weeks), 0.2, 0.3, and 0.4 mg/kg bid for 24 weeks. Placebo changed to 0.3 mg/kg bid at 12 weeks with all other groups changed to this dose at 24 weeks. After a total of 60 weeks of treatment, patients were followed for an additional 12 weeks.

Results:

There was a statistically significant improvement in 2 point reduction in SGA and PASI75 response by 12 weeks in the groups treated with ISA247, and this efficacy continued throughout 60 weeks of treatment. 79% of patients did not have a return of their disease and only 3.4% of patients overall experienced a psoriatic flare. Adverse events that occurred during the 60 weeks of treatment included *de novo* hypertension (11%), nasopharyngitis (11%), URI (6%), and headache (4%) as the most common adverse events, and the majority of these adverse events were mild in severity.

Discussion: Patients treated with ISA247 did not suffer from a psoriatic flare and the majority of patients did not have a return of disease 12 weeks after discontinuing therapy. Adverse events were mild in nature. A European Phase III study comparing ISA247 to cyclosporine and placebo in plaque psoriasis has commenced.

EADV 2007; May 16-20, 2007; Vienna, Austria

ISA247: Continued Safety and Efficacy After 60 Weeks of Continuous Therapy in Plaque Psoriasis by SGA

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Introduction: Cyclosporine is an efficacious agent in plaque psoriasis, but is limited due to dose-limiting toxicities. ISA247, a new calcineurin inhibitor (CNI), demonstrates increased potency with potentially less toxicity than cyclosporine. A 60 week Phase III study with ISA247 in moderate to severe plaque psoriasis has been completed.

Methods: 451 patients were enrolled in a Canadian Phase III study in 4 dose groups: Placebo (12 weeks), 0.2, 0.3, and 0.4 mg/kg bid for 24 weeks. Placebo changed to 0.3 mg/kg bid at 12 weeks with all other groups changed to this dose at 24 weeks. After a total of 60 weeks of treatment, patients were followed for an additional 12 weeks.

Results: Baseline SGA at entry was 3.2 ± 0.7 , and baseline PASI was 17 ± 6 . At 60 weeks, the percentage of patients with a 2-point reduction in SGA was 22%, and the PASI75 was 30%. Renal function remained stable throughout, and 4.4% of patients overall had a 30% decrease in calculated GFR. There were no differences in cholesterol, triglycerides, or other biochemical parameters. *De novo* hypertension (11%), nasopharyngitis (11%), URI (6%), and headache (4%), were the most common adverse events, and the majority of adverse events were mild in severity.

Discussion: ISA247 remains efficacious and well tolerated in the treatment of plaque psoriasis after 60 weeks of continuous therapy in this trial. A European Phase III study comparing ISA247 to cyclosporine and placebo in plaque psoriasis has commenced.

EADV 2007; May 16-20, 2007; Vienna, Austria

ISA247: Preliminary Results of a Phase IIB Multicentre, *Do Novo* Renal Transplant Trial

S. Busque¹, M. Laftavi², R. Gaston³, M. Goggins⁴, S. Mulgaonkar⁵ and P. Campbell⁶.

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Background

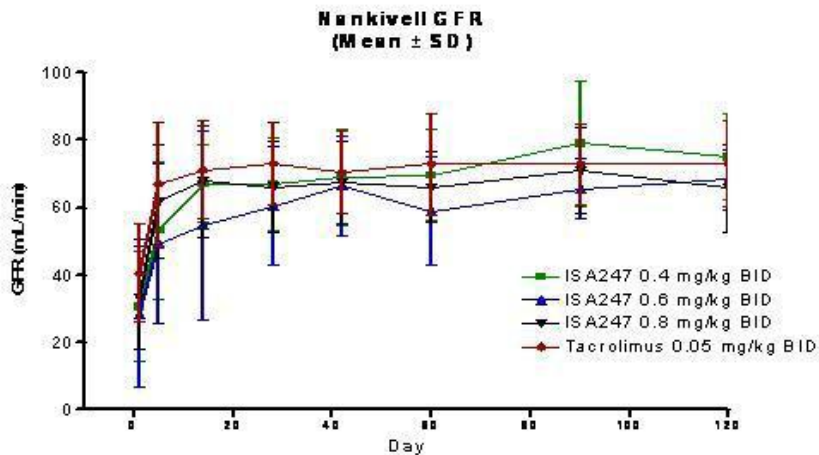
Nephrotoxicity remains the major limitation to calcineurin inhibitor (CNI) usage in transplantation and autoimmune disease. Other major complications include New Onset Diabetes Mellitus (NODM), hyperlipidemia and hypertension. ISA247 is a new generation CNI developed using a pharmacodynamic approach. A Phase IIa study showed that ISA247 is safe and efficacious in stable renal transplant patients, a Phase IIb study in *de novo* renal transplantation is being conducted comparing ISA247 to tacrolimus. This interim report consists of preliminary data from 120 patients enrolled with a planned enrollment of 332 patients.

Methods

This is a multicenter, open-label, concentration-controlled study. Patients are randomized to one of three oral ISA247 groups with a starting dose of 0.4 mg/kg bid, 0.6 mg/kg bid, 0.8 mg/kg bid, or oral tacrolimus at a starting dose of 0.05 mg/kg bid followed by titration to target trough concentrations. Additional immunosuppression with an anti IL-2 receptor antibody, mycophenolate mofetil and steroids. The primary objective is to demonstrate non-inferiority in biopsy proven acute rejection (BPAR) in *de novo* renal transplant patients at 6 months.

Results

	ISA247 0.4 mg/kg bid	ISA247 0.6 mg/kg bid	ISA247 0.8 mg/kg bid	Tacrolimus 0.05 mg/kg bid
Enrolled	28	26	31	35
Length of Follow-up (Months)	4.3 ± 2.5	4.5 ± 2.7	3.7 ± 2.2	3.9 ± 2.3
BPAR	14%	12%	0%	14%



Discussion

Early results in this dose ranging study would indicate that a low incidence of acute rejection was observed in all groups. So far no rejection episode has been observed in the higher dose ISA group. There appear to be no differences in renal function among groups. ISA247 continues to demonstrate a strong PK/PD correlation, which may facilitate ease of dosing to target concentrations. These preliminary data support ongoing enrollment in and extension of the trial to achieve one full year of observation. Data from a formal safety analysis will be presented at the meeting.

ATC 2007; May 5-9, 2007; San Francisco, CA

ISA247: A Novel Calcineurin Inhibitor (CNI) A Promising Safety Profile with Enhance Efficacy

Robert Gaston, MD¹, Stephan Busque, MD², Marcelo Cantarovich, MD³, Randall Yatscoff, PhD⁴ and Robert Huizinga, MSc⁴.

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Nephrotoxicity remains the major limitation to CNI usage in transplantation and autoimmune disease. ISA247 is a novel CNI with characteristics that indicate less propensity for a nephrotoxic effect. In humans, it has been studied in a Phase III psoriasis study, a Phase II stable renal transplant study and an ongoing Phase IIb *de novo* renal transplant study.

In psoriasis, the efficacy and safety of ISA247 was studied in 451 plaque psoriasis patients. Patients were randomized to receive placebo, ISA247 0.2, 0.3, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group was converted to 0.3 mg/kg/bid and all patients followed for an additional 12 weeks. Statistically significant efficacy was seen with both the 0.3 mg/kg and 0.4 mg/kg dose (PASI-75 26.4% and 49.1% respectively, $p < 0.05$), and the mean change in serum creatinine was negligible (3.0 ± 1.07 and 5.6 ± 0.95 $\mu\text{mol/L}$, respectively). There were no differences in cholesterol, triglycerides, or other biochemical parameters. Headache, diarrhea, and hypertension were the most common adverse events and were not related to dose.

In the concentration-controlled *de novo* renal transplant study, 332 patients are anticipated to be enrolled. Patients will be equally randomized to 1 of 3 doses of ISA247 (0.4, 0.6, 0.8 mg/kg bid) or tacrolimus (0.05 mg/kg bid). The primary objective is non-inferiority in biopsy proven acute rejection at 6 months. Thus far, 43 patients (31 ISA247, 12 FK506) have been enrolled. 2 episodes of acute rejection have been seen in the ISA247 arm (both Banff grades 1b) and two in the FK506 arm (1a and 2a) to date.

ISA247 is a systemic immunosuppressant that demonstrates statistically and clinically significant efficacy in psoriasis with minimal impact on kidney function. The *de novo* renal transplant trial is ongoing. One year data from the psoriasis study and exploratory data from the renal transplant study will be available for presentation at the meeting.

ASN 2006; November 14-19, 2006; San Diego, CA

ISA247 Remains a Safe and Efficacious Agent After 48 Weeks of Continuous Therapy: Interim Results of the SPIRIT Extension Study

Lyn Guenther, M.D.¹, Kirk Barber, M.D.², Ronald Vender, M.D.³, Ian Landells, M.D.⁴, Victoria Taraska, M.D.⁵, Yves Poulin, M.D.⁶, Nathalie Provost, M.D.⁷, Randall Yatscoff, Ph.D.⁸, Robert Foster, Ph.D.⁸ and SPIRIT Study Investigators⁹

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Introduction: ISA247, a new calcineurin inhibitor (CNI), demonstrates increased potency with potentially less toxicity than cyclosporine. A 36 week open-label extension study was offered to patients with moderate to severe plaque psoriasis who completed a 24 week randomized, double-blind, placebo-controlled Phase III study.

Methods: In the Phase III study, patients on placebo were changed to 0.3 mg/kg/bid after 12 weeks, patients on 0.2, 0.3, 0.4 mg/kg/bid were converted to 0.3 mg/kg/bid after 24 weeks. 310 patients enrolled in an extension study for an additional 36 weeks. Results after 48 weeks are below.

Results:

Parameter	Placebo x 12 wks	0.2 mg/kg x 24 wks	0.3 mg/kg	0.4 mg/kg x 24 wks
	then 0.3 mg/kg	then 0.3 mg/kg		then 0.3 mg/kg
Baseline PASI	17 ± 7	16 ± 5	17 ± 5	18 ± 6
PASI 75 Week 12	4.0 %	16.3%	25.2%	46.8%
PASI 75 Week 24	32.4%	16.3%	26.4%	49.1%
PASI 75 Week 48 (0.3 mg/kg)	42.6%	32.7%	41.8%	55.1%
GFR Change Week 12 (mL/min)	1.4 ± 0.8	1.2 ± 0.8	3.0 ± 1.1	5.6 ± 1.0
GFR Change Week 24 (mL/min)	-2.3 ± 9.5	-3.0 ± 8.1	-3.1 ± 11.1	-5.9 ± 10.1
GFR Change Week 48 (mL/min)	-4.0 ± 13.6	-2.8 ± 13.1	-7.1 ± 11.3	-1.5 ± 14.1

There was a statistically significant improvement in PASI 75 response and in a 2 point reduction in Static Global Assessment at 12 and 24 weeks in the groups treated with ISA247 when compared to placebo. The mean PASI reduction at 48 weeks was 64% in the low dose and 66% in the high dose. 4.4% of patients overall had a 30% decrease in calculated GFR. There were no differences in cholesterol, triglycerides, or other biochemical parameters. Headache (4-13%), diarrhea (1-9.5%), and hypertension (6-10%) were the most common adverse events, and the majority of adverse events were mild in severity.

Discussion: ISA247 is effective and well tolerated in the treatment of plaque psoriasis after 48 weeks of continuous therapy in this trial. A European Phase III study comparing ISA247 to cyclosporine and placebo in plaque psoriasis is planned to commence in June 2006.

EADV 2006; October 4-8, 2006; Rhodes, Greece

ISA247: A Novel Calcineurin Inhibitor – High Efficacy and Promising Safety Profiles

Steven Steinberg, MD¹, Ashok Jain, MD², Patricia Campbell, MBChB³, Goran B. Klintmalm, MD⁴, Anthony Jevnikar, MD⁵, Launa J. Aspeslet, PhD⁶, Robert T. Foster, PhD⁶, Derrick G. Freitag, PhD⁶, Robert B. Huizinga, MSc⁶, Norman Kneteman, MD³ and Randall W. Yatscoff, PhD⁶.

¹California Institute of Renal Research, San Diego, California, United States; ²University of Rochester, Rochester, New York, United States; ³University of Alberta, Edmonton, Alberta, Canada; ⁴Baylor University Medical Center, Dallas, Texas, United States; ⁵London Health Sciences Centre, London, Ontario, Canada and ⁶Isoteknika Inc., Edmonton, Alberta, Canada.

Background:

Calcineurin inhibitor (CNI) induced nephrotoxicity remains the major limitation in renal transplant and psoriasis treatments. ISA247 has been studied in a Phase III psoriasis study, a Phase II stable renal transplant study and an ongoing Phase IIb *de novo* renal transplant study.

Methods:

In the psoriasis study, the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ISA247 were studied in 451 plaque psoriasis patients. Patients were randomized to receive placebo, ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group was converted to 0.3 mg/kg/bid and all patients followed for an additional 12 weeks. In the concentration-controlled *de novo* renal transplant study, 332 patients are anticipated to be enrolled. Patients will be equally randomized to 1 of 3 doses of ISA247 (0.4, 0.6, 0.8 mg/kg bid) or tacrolimus (0.05 mg/kg bid). The primary objective is non-inferiority in biopsy proven acute rejection at 6 months. Patients will be evaluated at regular intervals for efficacy, renal function, biochemistry, and adverse events. The PK PD relationships of ISA247, tacrolimus, and MMF will be explored.

Results:

Statistically significant efficacy was seen with the 0.2 mg/kg, 0.3 mg/kg and 0.4 mg/kg dose (Week 12 PASI-75: 16.3%, 26.4% and 49.1% respectively, $p < 0.05$). The mean changes from baseline in serum creatinine were $1.1 \pm .84$, $2.1 \pm .77$ and 4.6 ± 0.89 $\mu\text{mol/L}$ respectively, while placebo change was $-2.4 \pm .77$ mol/L . There were no differences in cholesterol, triglycerides, or other biochemical parameters. Headache, diarrhea, and hypertension were the most common adverse events, and the majority of adverse events were mild in severity.

Conclusions:

ISA247 is a systemic immunosuppressant that demonstrates statistically and clinically significant efficacy in psoriasis with minimal changes to renal function. The renal transplant trial is presently enrolling. One year data from the psoriasis study and exploratory data from the renal transplant study will be presented at the meeting.

WTC 2006; July 22-27, 2006; Boston, MA

The Novel Immunosuppressant ISA247 Demonstrates a Different Metabolic Profile Than Cyclosporine A *In Vitro* and *In Vivo*

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¹Isotechnika Inc., Edmonton, Alberta, Canada; Department of Surgery, ²University of Alberta, Edmonton, Alberta, Canada.

Background:

ISA247 was designed to change cyclosporine metabolism at amino acid one to alter CsA toxicity. Metabolism of ISA247 and CsA were determined in human liver microsomes and in healthy volunteers.

Methods:

The velocity of metabolite formation was determined in human liver microsomes for ISA247 and CsA while only ISA247 metabolism was determined in healthy volunteers. ISA247 and metabolite concentrations were measured using validated LC/MS/MS methods.

Results:

The ISA247 metabolic profile was different from CsA. In microsomes, metabolites were formed by hydroxylation and N-demethylation. CsA metabolite formation rates were AM1 > AM4n > AM9 while ISA247 metabolite formation rates were IM4n > IM9 > IM1-Diol-1 indicating that ISA247 metabolism has been shifted away from amino acid one. Human data were identical based on AUC₍₀₋₁₂₎. ISA247 metabolism was IM9 > IM4n > IM1-Diol-1 while CsA demonstrates AM1 > AM9 indicating a shift of metabolism away from amino acid one. Importantly, Total Metabolite AUC₍₀₋₁₂₎/ISA247 AUC₍₀₋₁₂₎ was found to 0.5. For CsA, literature reports indicate a ratio range from 1.3 to 5.4 in kidney transplant patients.

Conclusions:

ISA247 demonstrates a different metabolic profile than CsA *in vitro* and *in vivo* shifting metabolism away from amino acid one resulting in a decreased metabolite load for ISA247 when compared to CsA.

WTC 2006; July 22-27, 2006; Boston, MA

Pharmacokinetics and Pharmacodynamics of ISA247 in a Phase III, Randomized, Multicentre, Double-Blind, Placebo-Controlled Study

Gupta, Aditya¹, Tomi, Zohair², Kunynetz, Rodion³, Guenther, Lyn⁴, Bourcier, Marc⁵, Yatscoff, Randall W.⁶, Mayo, Patrick⁶, Freitag, Derrick⁶, Foster, Robert T.⁶ SPIRIT Study Investigators⁷

¹Mediprobe Research Inc., London, ²NewLab Clinical Research Inc., St. John's, ³Probiity Medical Research Inc., Barrie, ⁴Guenther Dermatology Research Center, London, ⁵Clinique de Dermatologie, Moncton, ⁶Isotechnika Inc., Edmonton, ⁷Various Institutions

Introduction: Historically, the efficacy and safety of calcineurin inhibitors (CNI's) has been studied in psoriasis patients. However, the pharmacokinetics (PK) and pharmacodynamics (PD) of CNI's have not been studied or utilized to optimize dosing strategies. ISA247, a new CNI, is being developed using PKPD to optimize dosing strategies.

Methods: In a Phase III study, the efficacy, safety, PK and PD of ISA247 were studied in 453 plaque psoriasis patients. Patients were randomized to receive placebo, ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group was converted to 0.3 mg/kg/bid and the study continued for an additional 12 weeks. PASI75, ISA247 concentrations (PK), calcineurin inhibition (PD) and safety data were determined at weeks 4, 12 and 24.

Results:

Week 24: Pharmacokinetic-Pharmacodynamic Summary

Dose	C _{max} (ng/mL)	E _{max} (%CNI)	PASI75 (%)
Placebo (Week 12)	na	na	4.0 (0.2-7.9)
0.2 mg/kg	67.3 ± 39.0	32.6 ± 19.1	16.3 (9.0-23.6)
0.3 mg/kg	101.4 ± 51.0	43.0 ± 16.3	26.4 (18.0-34.8)
0.4 mg/kg	142.2 ± 82.2	49.5 ± 17.8	49.1 (39.7-8.4)

PKPD (Mean ± SD), PASI75 (Mean ± 95% Confidence Intervals)

ISA247 concentration highly correlated with calcineurin inhibition (r = 0.79) and mean E_{max} highly correlated with the mean percent reduction in PASI (r = 0.86).

Conclusions: PKPD data suggest calcineurin inhibition > 40% is associated with good efficacy in plaque psoriasis.

CDA 2006; June 27 – July 2, 2006; Winnipeg, MB

24 Week Results of a Phase III Randomized, Double-Blind, Multicentre, Placebo-Controlled Study of ISA247 in Plaque Psoriasis

Langley, Richard¹; Bissonnette, Robert²; Searles, Gordon³; Shear, Neil⁴; Thomas, Richard⁵; Yatscoff, Randall⁶; Aspeslet, Launa⁶; Huizinga, Robert⁶; Papp, Kim⁷; SPIRIT Study Group⁸

¹Eastern Canada Cutaneous Research Associates, Halifax;² Innovaderm Research Inc., Montreal;
³Western Canada Dermatology Research, Edmonton; ⁴Ventana Clinical Research Corporation, Toronto;
⁵Derm Research @ 888 Inc., Vancouver; ⁶Isotechnika Inc., Edmonton; ⁷Probit Medical Research Inc., Waterloo; ⁸Various Institutions

Introduction

ISA247, a new calcineurin inhibitor (CNI), demonstrates increased potency with potentially less toxicity than cyclosporine. A Phase III multicentre, Canadian study was conducted to determine the safety and efficacy of ISA247 in patients with moderate to severe plaque psoriasis.

Methods

Plaque psoriasis patients (n = 451) with ≥10% body surface area involvement were enrolled. Patients were randomized to receive placebo, ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group was converted to 0.3 mg/kg/bid and all patients were followed for a total of 24 weeks. The primary objective was to determine the proportion of subjects achieving a PASI-75 at 12 weeks in each dosing group.

Parameter	Placebo	0.2 mg/kg	0.3 mg/kg	0.4 mg/kg
Baseline PASI	17 ± 7	16 ± 5	17 ± 5	18 ± 6
PASI 75 Week 12	4.0%	16.3%	25.2%	46.8%
PASI 75 Week 24	32.4%	16.3%	26.4%	49.1%
SCr Change Week 24 (µmol/L)	1.4 ± 0.77	1.2 ± 0.75	3.0 ± 1.07	5.6 ± 0.95
GFR Change Week 24 (mL/min)	-2.3 ± 9.5	-3.0 ± 8.1	-3.1 ± 11.1	-5.9 ± 10.1

Patient demographics were similar between groups. There was a statistically significant difference in PASI 75 response and 2 point reduction in Static Global Assessment at weeks 12 and 24 in the group treated with ISA247 when compared to placebo. The maximal mean increase in serum creatinine was 5.6 µmol/L at 24 weeks in the highest dose group. There were no differences in cholesterol, triglycerides, or other biochemical parameters. Headache, diarrhea, and hypertension were the most common adverse events, and the majority of adverse events were mild in severity.

Conclusions

ISA247 is effective and well tolerated in the treatment of plaque psoriasis at 24 weeks.

CDA 2006; June 27 – July 2, 2006; Winnipeg, MB

A Phase III, Randomized, Multicentre, Double-Blind, Placebo-Controlled, Quality of Life Study of ISA247 in Plaque Psoriasis Patients

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Introduction:

Psoriasis has a long-term detrimental impact on patient's Quality of Life (QoL). Investigations of new treatment options in psoriasis should include efficacy as well as impact on patient QoL. ISA247 is a new calcineurin inhibitor (CNI) demonstrating increased potency in association with decreased toxicity as compared to other CNI's. A Phase III study was conducted to determine the impact of ISA247 on the QoL indicators in patients with stable moderate to severe plaque psoriasis.

Methods:

451 patients were randomized to receive placebo, ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group converted to 0.3 mg/kg/bid and the study continued for an additional 12 weeks. QoL measures included the Dermatology Life Quality Index (DLQI) which measures 10 domains, and the Psoriasis Disability Index (PDI) which measures 5 domains.

Results:

There was a statistically significant improvement in all domains by 12 weeks and this was maintained for the 24 weeks. For example, DLQI scoring of "psoriatic symptoms" (itchy, sore, painful or stinging) and "selfconsciousness" were both improved dramatically, with an increase in the percentage of patients reporting little or not at all from 32% and 44% (symptoms and self-consciousness respectively) to 81% and 88% at week 12, to 86% and 89% at week 24. The PDI measurement of "work or school" improved by decreasing from a mean of 1.2 to 0.4 and 0.4 at weeks 12 and 24 respectively.

Conclusions:

ISA247 represents a new CNI for the treatment of stable plaque psoriasis with significant improvements in QoL for psoriatic patients. Two further Phase III studies are planned for Europe and North America

CDA 2006; June 27 – July 2, 2006; Winnipeg, MB

A Phase III, Randomized, Multicentre, Double-Blind, Placebo-Controlled Quality of Life Study of ISA247 in Plaque Psoriasis Patients

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¹Lynderm Research Inc., ²Probit Medical Research Inc., ³The Guenther Dermatology Research Centre, ⁴Siena Medical Research Corp.

Introduction:

Psoriasis has a long-term detrimental impact on patient's quality of life (QoL). Efficacy measures of new agents in psoriasis should include the impact of these agents in QoL measures. ISA247 is a new calcineurin inhibitor (CNI) demonstrating increased potency in association with decreased toxicity, compared with other CNi's. A randomized, double-blind, placebo-controlled, parallel-group phase III study was conducted to determine the impact of ISA247 on the QoL indicators in patients with moderate to severe plaque psoriasis.

Methods:

Four hundred fifty-three stable plaque psoriasis patients with $\geq 10\%$ body surface area involvement were enrolled. Patients were randomized to receive placebo, or ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid and the study continued for an additional 12 weeks. The primary objective was to determine the proportion of subjects achieving a PASI75 at 12 weeks in each dosing group. QoL measures included the DLQI and the PDI taken at each visit.

Results:

Safety and efficacy results are currently blinded. A blinded interim analysis conducted with approximately 75% of patients at 12 weeks, demonstrated a mean PASI decrease of 38%. Blinded treatment-related adverse events include headache (6.7%), diarrhea (3.5%), nausea (3.5%), arthralgia (2.7%), myalgia (1.1%), and back pain (1.1%). Gingivitis and dyspepsia were seen in less than 1% of patients.

Conclusions:

ISA247 represents a new CNI for the treatment of stable plaque psoriasis. Blinded interim results demonstrate efficacy with an acceptable adverse event profile. Unblinded QoL and adverse event data will be presented.

AAD 2006; March 3-7, 2006; San Francisco, CA

Pharmacokinetics and Pharmacodynamics of ISA247 in a Phase III Randomized, Multicenter, Double-Blind, Placebo-Controlled Study

Wasel N¹, Gupta A², Tomi Z³, Papp K⁴

¹Probity Medical Research Inc., ²Mediprobe Research, ³NewLab Clinical Research., ⁴Probity Medical Research Inc.

Introduction:

Trough measurements of cyclosporine have poor correlation with AUC or efficacy. Utilization of a pharmacodynamic marker may allow for improved patient management. ISA247 is a new calcineurin inhibitor (CNI) demonstrating increased potency in association with decreased toxicity as compared to other CNi's. A randomized, double-blind, placebo-controlled, parallel group Phase III study was conducted to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of ISA247 in patients with moderate to severe plaque psoriasis.

Methods:

453 stable plaque psoriasis patients with $\geq 10\%$ body surface area involvement were enrolled. Patients were randomized to receive placebo, ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group was converted to 0.3 mg/kg/bid and the study continued for an additional 12 weeks. The primary objective was to determine the proportion of subjects achieving a PASI-75 at 12 weeks in each dosing group. ISA247 and calcineurin trough measurements along with 2-hour postdose sampling (C_2) were taken in all patients at weeks 4, 12, and 24. A subset of patients (20 patients per group) participated in an AUC_{0-4} PK/PD study at weeks 4, 12, and 24.

Results:

Safety and efficacy results are currently blinded. A blinded interim analysis, conducted with approximately 75% of patients at 12 weeks, demonstrated a mean PASI decrease of 38%. Median maximum calcineurin inhibition is approximately 50%. Presentation of the unblinded pharmacokinetic and pharmacodynamic data will take place at the AAD's 64th Annual Meeting.

Conclusions:

ISA247 represents a new CNI for the treatment of stable plaque psoriasis. Blinded interim results demonstrate an acceptable pharmacodynamic response using the calcineurin assay. Using a pharmacodynamic marker instead of trough measurements may allow for individualization of patient dosing and a superior method for dosing CNI agents.

AAD 2006; March 3-7, 2006; San Francisco, CA

A Phase III, Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of ISA247 in Plaque Psoriasis Patients

Papp K¹, Langley R², Bissonnette R³, Rosoph L⁴

¹Probit Medical Research Inc., ²Eastern Canada Cutaneous Research Associates Ltd., ³Innovaderm Research Inc., ⁴North Bay Dermatology Centre

Introduction:

ISA247 is a new calcineurin inhibitor (CNI) demonstrating increased potency in association with potentially decreased toxicity as compared other CNI's. The utility of cyclosporine (CsA) is directly limited in the treatment of plaque psoriasis by its renal toxicity profile. Based on previous Phase II data, a randomized, double-blind, placebo-controlled, parallel-group Phase III study was conducted to determine the safety and efficacy of ISA247 in patients with moderate to severe plaque psoriasis.

Methods:

453 stable plaque psoriasis patients with $\geq 10\%$ body surface area involvement were enrolled. Patients were randomized to receive placebo, ISA247 0.2 mg/kg/bid, 0.3 mg/kg/bid, or 0.4 mg/kg/bid for 12 weeks. At the end of 12 weeks the placebo group was converted to 0.3 mg/kg/bid and the study continued for an additional 12 weeks. The primary objective was to determine the proportion of subjects achieving a PASI-75 at 12 weeks in each dosing group. Secondary objectives included the safety and tolerability of ISA247, the pharmacokinetics and pharmacodynamics (calcineurin inhibition) of ISA247 with chronic dosing and to evaluate the effect of ISA247 on patient quality of life. Safety analyses included renal function (glomerular filtration rate and serum creatinine), hypertension, hyperlipidemia, and liver function tests.

Results and Conclusions:

Safety and efficacy results are currently blinded. A blinded interim analysis, conducted with approximately 75% of patients at 12 weeks, demonstrated a mean PASI decrease of 38%. The highest mean change in serum creatinine in any of the dosing groups was 5.6% above baseline which is within normal analytical and physiological variation. A total of 5 (2%) patients were withdrawn for changes in renal function, defined as a confirmed 30% decrease in glomerular filtration rate. Clinical blood work, including serum lipids and liver function tests, has remained stable. Median maximum calcineurin inhibition is approximately 50% in the blinded data set. Patients completing this study are presently being enrolled into a 36-week, open-label extension using 0.3 mg/kg/bid of ISA247. The unblinded efficacy and safety data in the primary efficacy study are presented.

AAD 2006; March 3-7, 2006; San Francisco, CA

ISA247: A Calcineurin Inhibitor That Shows Minimal Impact on Renal Function in a Phase III Trial

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Isotechnika, Edmonton, AB, Canada.

Background

Calcineurin inhibitor (CNI) induced nephrotoxicity remains the major limitation in renal transplant and psoriasis patients. In a large phase III Canadian psoriasis trial the safety and efficacy of ISA247 was evaluated using doses anticipated for renal transplantation. Methods: 453 patients were enrolled into this randomized, double-blind trial to examine the efficacy of three doses of ISA247 (0.2 mg/kg, 0.3 mg/kg and 0.4 mg/kg) administered BID compared to placebo in a 1:1:1:1 fashion. Patients were evaluated for 12 weeks at regular intervals for efficacy, renal function (MDRD GFR, serum creatinine), biochemistry, adverse events, pharmacokinetics and calcineurin inhibition as a pharmacodynamic marker.

Results

Statistically and clinically significant efficacy was seen with the 0.3 and 0.4 mg/kg BID doses. The mean calcineurin inhibition for these doses was 44% and 55%, respectively. Treatment-related adverse events in patients receiving ISA247 were similar to those receiving placebo. Additionally, there were no clinically significant changes in blood pressure, cholesterol, triglycerides and infectious complications. Minimal changes to renal function were observed at the high dose. However, these were not statistically significant ($p=NS$).

Parameter	Placebo	0.2 mg/kg	0.3 mg/kg	0.4 mg/kg
Baseline SCr (umol/L)	85.3	81.6	84.6	84.3
Mean Change at 12 weeks	-2.1 ± 0.88	1.3 ± 0.89	2.4 ± 0.87	4.4 ± 1.01
%Change	-2.5	1.6	2.8	5.2
Baseline MDRD GFR (mL/min)	86	87	91	89
Mean Change at 12 weeks	2.1 ± 10.2	-1.4 ± 8.5	-3.4 ± 10.9	-5.1 ± 9.7
%Change	2.5	-1.6	-3.7	-5.7

Conclusions: ISA247 is a systemic immunosuppressant agent that demonstrated statistically and clinically significant efficacy in psoriasis with non-statistical changes to renal function. The doses utilized in this trial are similar to those anticipated as maintenance doses in renal transplantation. A Phase IIb study in *de novo* renal transplantation is presently underway.

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