A Phase I/II Study of Vicinium™ Given by Intravesical Administration in Patients with Superficial Transitional of the Bladder: Phase I Final Results

Abstract #91750

M.Jewett[c], N.Jones[a], W. Cuthbert[a], M. Rasamoelisolo[b], J. Entwistle[b], G. MacDonald[b] and N.Glover[a]

Viventia Biotech Inc., Toronto, ON[a], Viventia Biotech Inc., Winnipeg, MB[b], and Princess Margaret Hospital, Division of Urology, Toronto, ON[c]

VIVENTIA BIOTECH INC.

Updated Abstract

Background: Vicinium™ is a fusion protein comprised of a humanized fragment scFv, specific for EpCAM (epithelial cell adhesion molecule), and a truncated form of *Pseudomonas* exotoxin A. EpCAM is highly expressed on carcinoma cells including superficial transitional cell carcinomas (TCC) of the bladder. Vicinium specifically targets and kills EpCAM positive tumors. Results from a Phase I/II trial where Vicinium was instilled into the bladders of patients with superficial TCC of the bladder showed the drug to be very well tolerated and showed promising clinical results.

Methods: 64 patients with EpCAM positive superficial TCC of the bladder, Ta, Tis or T1 Grade 2 or Grade 3 who were refractory or intolerant to BCG therapy were entered into the study. Dosing comprised a minimum of 3 subjects per dose level through 12 escalating doses. Vicinium was given once/week for 6 consecutive weeks by intravesical administration into the bladder via a catheter at escalating dose levels of 0.1, 0.2, 0.33, 0.66, 1.32, 2.64, 5.28, 10.56, 13.73, 17.85, 23.2 and 30.16 mg/week. All toxicities were assessed according to the NCI CTC AE v3. Blood samples were collected at different times in the study to determine systemic drug exposure and to assess immunogenicity. Efficacy was explored via biopsy, cystoscopy, urine cytology and FISH.

Results: Vicinium was very well tolerated at all doses. No maximum tolerated dose (MTD) was reached. Almost all (>98%) of the patients screened were positive for the EpCAM antigen. Pharmacokinetic analysis showed no evidence of Vicinium in the circulation of any of the patients. Most patients, in particular at the higher doses, demonstrated a positive clinical benefit following treatment.

Conclusions: Vicinium dosed on a weekly basis for 6 weeks was very well tolerated at all dose levels. Moreover, although this study was primarily designed to evaluate safety and tolerability, Vicinium showed promising efficacy results. The early clinical benefit observed with Vicinium strongly supports its development as a promising therapy for superficial transitional cell carcinoma of the bladder.

Objectives

Primary
- To assess the safety and maximum tolerated dose level of intravesical administration of Vicinium in subjects with BCG refractory/intolerant transitional cell carcinoma (TCC) of the bladder.

Secondary
- To explore the anti-tumor activity of Vicinium administered by this dosage schedule and route of administration.

Background

- Bladder cancer is the seventh most common cancer worldwide (58,000 new cases diagnosed annually in North America)
- Vicinium is a recombinant protein engineered from the fusion of a humanized scFv antibody fragment specific for the epithelial cell adhesion molecule, EpCAM, to a truncated form of *Pseudomonas* Exotoxin A (ETA)
- EpCAM is a cell surface marker that is highly expressed on the cell surface of carcinoma cells of epithelial origin, including transitional cell carcinomas of the bladder, and has limited normal tissue expression

Mechanism of action:
- Vicinium selectively binds to EpCAM-positive tumors and is internalized by the tumor cell through an endocytic pathway
- The ETA portion of Vicinium then traffics to the endoplasmic reticulum, where it shuts down protein synthesis resulting in tumor cell death via apoptosis

Trial Design

Phase I/II, open-label, multicenter (N=13), safety and tolerability study in ascending dose cohorts

- 12 dose cohorts:
  - 0.1 mg (N=4), 0.2 mg (N=3), 0.33 mg (N=5), 0.66 mg (N=5),1.32 mg (N=3), 2.64 mg (N=5), 5.28 mg (N=6),10.56 mg (N=5), 13.73 mg (N=3), 17.85 mg (N=7), 23.20 mg (N=10) and 30.16 mg (N=8)
- Weekly dosing for 6 weeks
- Patients assessed by cystoscopy, cytology, and (biopsy, where indicated) at 3 months prior to entering post-study surveillance
- Dose escalation decision after review of AEs and laboratory data, evaluated after 3 weeks of treatment
- Safety assessed from AEs, lab results, physical examination, vital signs, and ECG
- Tumor response to treatment assessed by cystoscopy, cytology, (biopsy, where indicated), and FISH as a research test

Eligibility

Principal Inclusion Criteria
- Histologically confirmed diagnosis of superficial Grade 2 or Grade 3 TCC (Ta, Tis, T1) of the bladder
- TCC that has recurred following at least 1 complete cycle of intravesical BCG treatment within the last 2 years
- Immunohistochemically confirmed EpCAM-positive TCC
- Adequate hepatic, hematological and renal function

Principal Exclusion Criteria
- Evidence of muscle-invasive (T2, T3) nodal involvement or distal metastases
- Subjects with either adenocarcinoma or squamous cell carcinoma of the bladder
- History of upper tract TCC or disease involving the prostatic ducts or stroma or history of pelvic malignancy
- Hydronephrosis or any clinically significant abnormalities of the upper urinary tract
- BCG therapy within 6 weeks prior to the start of Vicinium dosing

Patient Baseline Characteristics (N=64)

Age - median (range)	69 years (50-87)
Gender	
Male	50 (78%)
Female	14 (22%)
Disease Duration	
1-4 years	43 (67%)
> 4 years	21 (33%)
Number or Recurrences	
< 2	3 (5%)
≥ 2	61 (95%)
Prior BCG cycles	
0	2 (3%)
1	27 (42%)
2 or more	35 (55%)
Last BCG cycle	
> 6 months	40 (65%)
≤ 6 months	22 (35%)

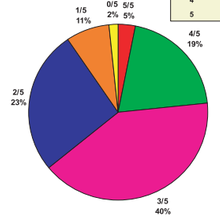
Baseline Histology

Stage	Grade 1	Grade 2	Grade 3	Total
Ta		25	5	30
T1		10	7	17
Tis				17

Risk Factors at Baseline

- Aggressive histology (Tis; T1; Ta Grade 3)
- ≥ 2 recurrences
- Disease history > 4 years
- ≥ 2 BCG failures
- Last BCG failure < 6 months

Number of Criteria	Number of Patients
0	1
1	7
2	15
3	26
4	12
5	3



- 98% of patients had at least one factor associated with higher risk of disease progression
- 64% of patients had 3 or more risk factors associated with a higher risk of disease progression

Adverse Events Related to Study Drug

20 Patients (31%) experienced Adverse Events Related to Study Drug

Local Adverse Events

Local Adverse Drug Events	Grade 1	Grade 2	Grade 3
Urinary frequency/urgency	4	2	
Painful/difficult urination (dysuria)	8	2	
Hematuria	5	1	1

Systemic Adverse Events

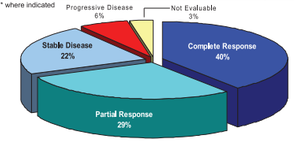
Systemic Adverse Drug Events	Grade 1	Grade 2	Grade 3
Arthralgia		1	
Chills/Fever	2	1	
Dizziness	2		
Fatigue	5		
Myalgia	2	1	
Nausea		1	

- Vicinium was safe and well-tolerated
- No maximum tolerated dose established
- No dose dependent AE profile observed
- Side effect profile appears very favorable in comparison to the known side effects of intravesical chemotherapy or BCG treatments

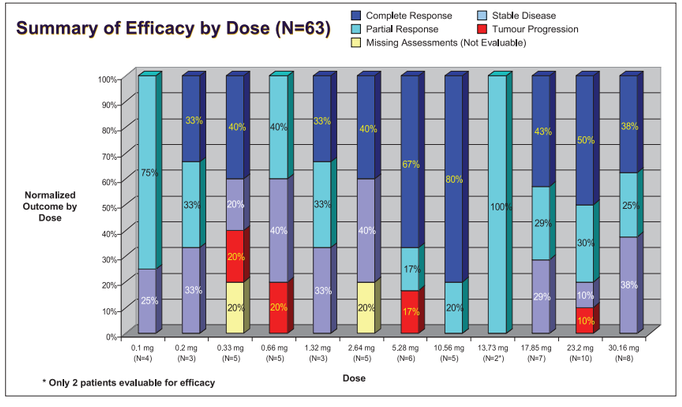
Summary of Overall Efficacy at Final Visit (N=63)

Disease Response	Cystoscopy	Biopsy	Cytology
Complete Response (1)	Negative	Negative*	Non-positive
Complete Response (2)	Positive	Negative*	Negative
Partial Response (1)	Negative or Positive	Negative*	Non-negative
(2)	Positive	No change	Negative
(3)	Positive	Improvement in Stage	
Stable Disease	Positive	No change	Non-negative
Progressive Disease	Positive	Worsening in Stage	

* where indicated



Summary of Efficacy by Dose (N=63)



* Only 2 patients evaluable for efficacy

- Vicinium administered intravesically demonstrated promising efficacy outcomes across doses
- Efficacy profile has apparent dose dependencies requiring further investigation
- 6% progressed (98% of patients had at least one factor at baseline associated with a higher risk of disease progression)

Pharmacokinetics

Vicinium plasma concentration was measured using an MTS-based assay to determine cytotoxicity against the SCCHN cell line Cal-27.

None of the 61 patients tested had detectable levels of Vicinium in their plasma, indicating no leakage outside the bladder.

Summary and Conclusions:

- Vicinium, a recombinant fusion protein specific to EpCAM, can be safely administered to patients with superficial transitional cell carcinoma of the bladder via intravesical administration
- Vicinium was safe and well tolerated
- No maximum tolerated dose reached
- 6% progressed (98% of patients had factors at baseline associated with a higher risk of disease progression
- A 69% response rate (complete + partial response) was observed
- These promising results support further clinical development of Vicinium

Participating Investigators

Dr. Michael Jewett
Princess Margaret Hospital, Toronto, ON

Dr. Louis Lacombe
Centre de Recherche, CHUQ-L'Hôtel-Dieu de Québec, Québec City, QC

Dr. Fred Saad
CHUM/Hôpital Notre-Dame, Montreal, QC

Dr. Armen Aprikian
Montreal General Hospital, Montreal, QC

Dr. Laurence Klotz
Sunnybrook & Women's College Health Sciences Centre, Toronto, ON

Dr. Joseph Chin
London Health Sciences Centre, London, ON

Dr. Cal Andreou
Andreou Research, Surrey, BC

Dr. Jack Barkin
The Female/Male Health Centre, Toronto, ON

Dr. Richard Casey
The Female/Male Health Centre, Oakville, ON

Dr. Bernard Goldfarb
Northbay, ON

Dr. Joseph Zadra
The Female/Male Health Centre, Barrie, ON

Dr. Morrie S. Liquornik
Mor Urology Inc., Newmarket, ON

Dr. William R. Love
Urology Resource Centre, Burlington, ON