



[NCT02020291](#)

Preliminary Report: Phase I Dose Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Profiles of Foxy-5 in Patients with Metastatic Breast, Colon or Prostate Cancer

November 6th, 2015



Background

Most current anti-cancer therapeutic drugs are targeting the proliferation and/or survival of cancer cells while very few drugs are aimed at specifically targeting the dissemination process.

Several reports have demonstrated that low-levels or lack of Wnt-5a protein expression in primary breast-, colon-, and prostate cancer tissues correlate with shortened patient recurrence-free survival and overall survival, pointing to a biological role of Wnt5a signaling in the dissemination process of cancer cells.

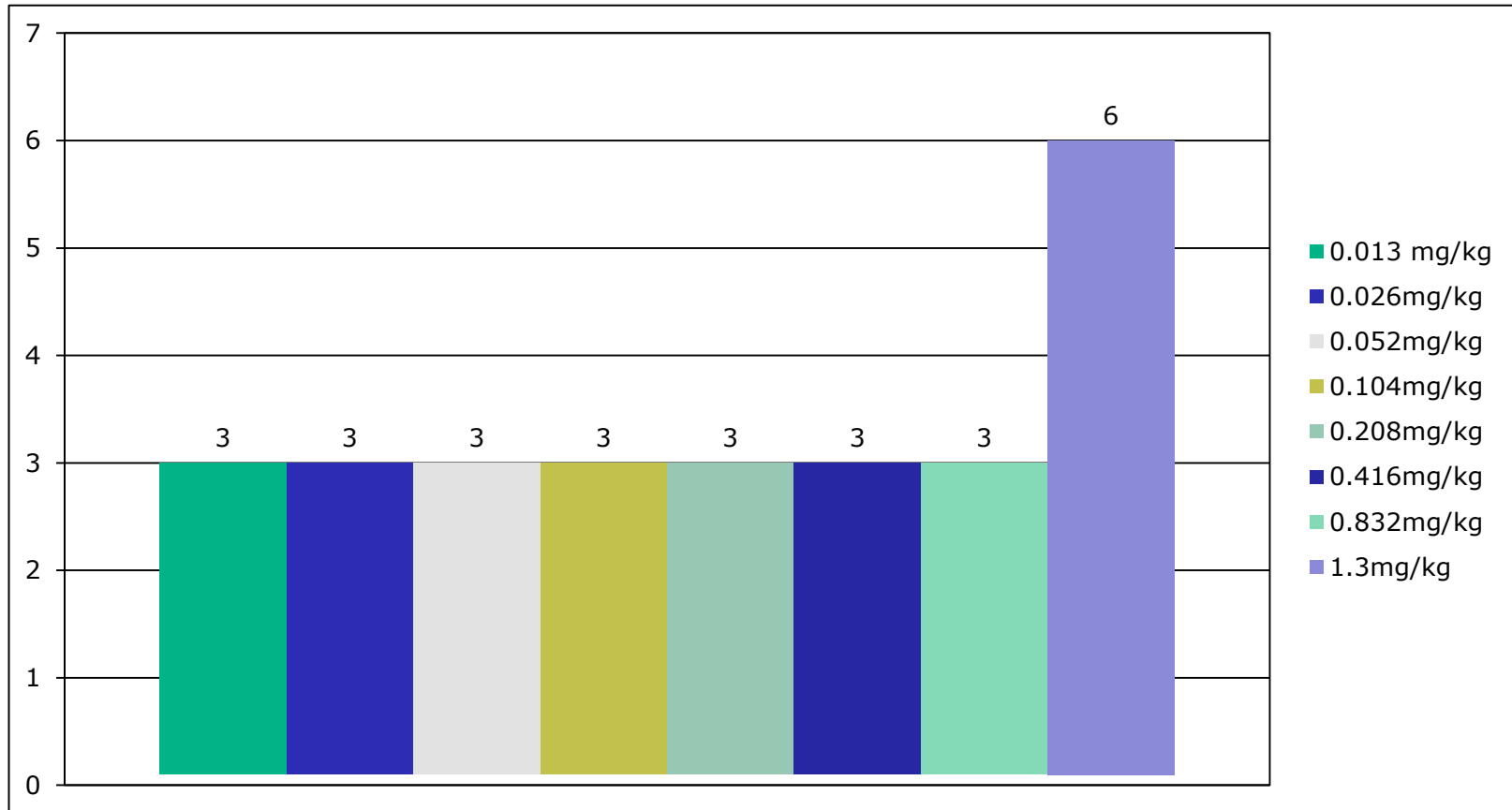
Therefore, we developed two peptides, one being a Wnt-5a agonist (Foxy-5) and one being a Wnt-5a antagonist (Box-5). The Foxy-5 is a formulated Wnt-5a-derived hexapeptide that mimics the ability of the Wnt-5a molecule to impair cancer cell migration and invasion *in vitro* and significantly reducing the formation of distant metastases *in vivo* in mouse models of breast cancer.

In addition, toxicology studies in rats and dogs with a final dose well exceeding the dose previously used in the mouse models showed no Foxy-5-induced toxic reactions. Based on all these pre-clinical data we initiated a clinical phase 1 study with the primary objective to evaluate the safety and tolerability of Foxy-5. All eligible patients were pre-screened for Wnt-5a immunoreactivity in archival tumor tissue and from dose level 7 and onwards only patients with negative or low level Wnt-5a expressing metastatic breast-, colon-, or prostate cancer were enrolled in the study.

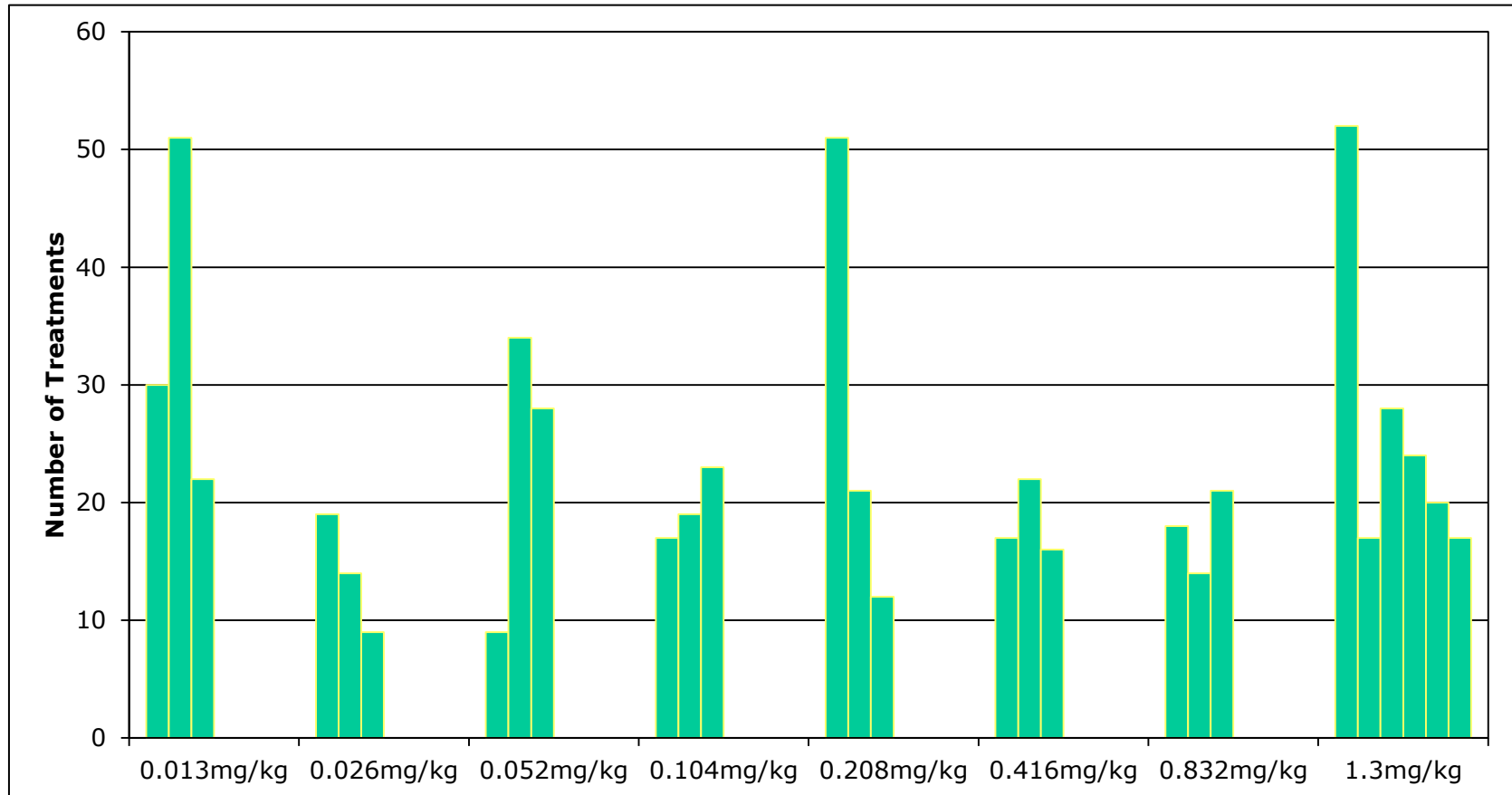
Trial Design

- **Open-label, Phase 1, Standard 3+3 Dose escalation cohort design:**
 - Cohort 1 - 0.013mg/kg
 - Cohort 2 - 0.026mg/kg
 - Cohort 3 - 0.052mg/kg
 - Cohort 4 - 0.104mg/kg
 - Cohort 5 - 0.208 mg/kg
 - Cohort 6 - 0.416 mg/kg
 - Cohort 7 - 0.832 mg/kg
 - Cohort 8 - 1.3 mg/kg
- **31 (27 evaluable) patients with metastatic breast-, colon- or prostate cancer.**
- **Patients received one intravenous slow infusion of Foxy-5 three times weekly for 3 weeks (1 cycle).**
- **Foxy-5 treatment continued at the Investigator's discretion.**

Number of Patients completed per protocol



Number of Exposures to Foxy-5



Primary Objective

To evaluate the safety and tolerability of treatment with Foxy-5.

Primary Safety Variables:

- Adverse events
- Clinical laboratory parameters
- Physical examination findings
- Vital signs
- ECG

Results

- **Foxy-5 appears safe and well tolerated, with no dose limiting toxicities were observed at any dose.**

Secondary Objectives

To determine the maximum tolerated dose and dose-limiting toxicity of Foxy-5.

- **Secondary Safety Variables**
 - Toxicity assessed by NCI Common Toxicity Criteria for Adverse Events (CTCAE), DLT defined as any of the adverse events defined in these criteria that were at least possibly related to the study medication.

Results

- **No dose limiting toxicities were observed and therefore no maximum tolerated dose (MTD) could be defined.**

Serious Adverse Events (SAEs)**

System Organ Class (SOC)	n
General disorders and administration site conditions	4
Infections and infestations	3
Gastrointestinal disorders	2
Cardiac disorders	1
Nervous system disorders	1
Reproductive system and breast disorders	1
Vascular disorders	1

- **The most prevalent SAEs were general disorders and administration site conditions (pyrexia was the most common)**
- **3 SAEs were rated as possibly related to treatment; they were chest pain, pyrexia and hypertension**
- **None of these SAEs were considered to be dose limiting**

Secondary Objectives cont.

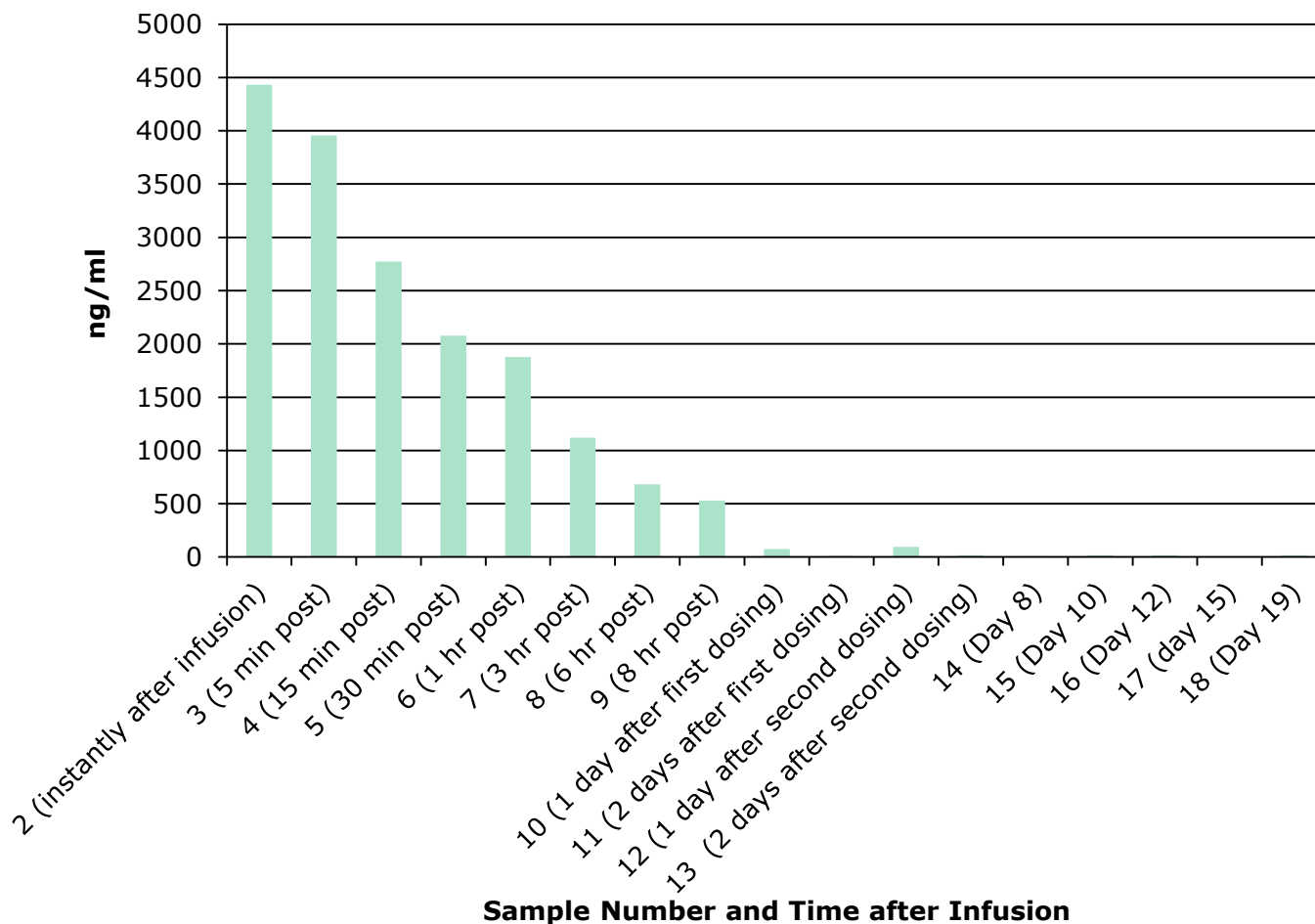
Pharmacokinetic profile of Foxy-5.

Results

- Results are presently available up to and including dose cohort 6 (0.416 mg/kg).
- Foxy-5 could be detected in the blood, with highest levels within 5 minutes after infusion.
- Foxy-5 concentration was below the lower limit of quantitation 2 days after first infusion in cohorts 1 and 2 and undetectable in cohort 3 by the start of the second week of treatment. In cohorts 4-6, Foxy-5 could be detected in the blood throughout the treatment cycle (3 weeks, 9 infusions) and the half-life of Foxy-5 was less than 1hr post infusion.

Secondary Objectives cont.

Pharmacokinetic profile of Foxy-5 in a representative patient from dose level 6.



Secondary Objectives cont.

To characterise the pharmacodynamic profile of Foxy-5 by assessing anti-tumour activity of Foxy-5 in any of the below parameters:

- **Circulating tumor cells before and during Foxy-5 treatment**
- **NGAL plasma content before and during Foxy-5 treatment**
- **mRNA expression in tumors before and during Foxy-5 treatment**
- **Wnt-5a tumor cell content before and during Foxy-5 treatment**
- **CT scans before and during Foxy-5 treatment**

CTC Results

Cohort	Patient No.	Diagnosis	Wnt-5a status	Day 1	Day 12	Day 19
5	01-0016	C. Prostate	loss or reduced	69 & 70	49 & 56	63 & 66
	02-0001	C. Bladder	normal level	94 & 92	276 & 302	267 & 215
6	02-0002	C. Colon	normal level	9 & 13	12 & 10	29 & 33
	01-0017	C. Colon	normal level	2 & 1	2 & 2	2 & 2
	01-0018	C. Prostate	loss or reduced	826	**	**
7	01-0019	C. Breast	loss or reduced	98 & 100	161 & 145	338
	02-0004	C. Colon	loss or reduced	10 & 11	**	10 & 13
	02-0005	C. Colon	loss or reduced	1 & 4	1 & 2	6 & 7
8	01-0020	C. Prostate	loss or reduced	1 & 1	2 & 1	1 & 4
	01-0021	C. Prostate	loss or reduced	18 & 12	15 & 26	36 & 36
	02-0006	C. Breast	loss or reduced	0	0 & 0	0 & 0
	02-0007	C. Colon	loss or reduced	5 & 3	5 & 6	**
	01-0023	C. Prostate	loss or reduced	2	2 & 3	5 & 7
	01-0024	C. Colon	loss or reduced	1 & 1	5 & 6	8 & 14
	01-0025	C. Prostate	loss or reduced	87 & 106	91 & 94	83 & 93
	01-0026	C. Colon	loss or reduced	0 & 0	0 & 0	0 & 0

CTC counts are the sum of cells entering the blood stream and cells leaving the blood stream.

**Assay not performed

Secondary Objectives cont.

Biomarkers

- To characterize the profile for the biomarker NGAL in blood
Results not yet available.
- To characterize the mRNA expression (genome-wide) and the protein expression by IHC analysis of Wnt-5a in voluntary tumour biopsies obtained prior to Day 1 and after 2 weeks treatment on Day 12.

Results not yet available.

CT Scan Results

Response after weeks (or EOT)			
Cohort	Number of Patients	8 Week (N of treatments)	16 Week (N of treatments)
1	2	Progressive disease (22;33)	Progressive disease (51)
	1	Stable disease (24)	
2	3	Progressive disease (9;14;19)	
3	1	Progressive disease (28)	Progressive disease (34)
	1	Stable disease (24)	
4	3	Progressive disease (17;19;23)	
5	2	Progressive disease (12;21)	Stable disease (51)
	1	Stable disease (24)	
6	3	Progressive disease (16;17;22)	
7	3	Progressive disease (14;18;21)	
8	5	Progressive disease (17;17;20;24)	Stable disease (52)
	2	Stable disease (24,28)	

Conclusions

- **We are very pleased that the phase 1 study with Foxy-5 is finalized. The results from the study demonstrate that from a toxicological point of view Foxy-5 is a safe and well tolerated drug with no dose limiting toxicities observed at any dose. This is in line with our rat and dog toxicity studies and will facilitate combination treatment with Foxy-5 and other anti-cancer drugs in the future.**
- **Foxy-5 could be detected in blood, with highest levels within 5 minutes after infusion. In cohorts 4-6, Foxy-5 could be detected in the blood throughout the treatment cycle (3 weeks, 9 infusions) and the half-life of Foxy-5 was less than 1hr post infusion.**
- **CTC counts are difficult to evaluate, since Foxy-5 impairs at least two different processes and that are release of tumor cells from tumor tissues (decreasing the number of CTC's) and the passage of cancer cells out of the blood stream (increasing the number of CTC's). We will in future studies use additional technologies for CTC measurements.**

Conclusions cont.

According to the protocol, each patient should receive 9 infusions of Foxy-5 in order to be evaluable. Treatment could continue based on the physician's discretion.

- As measured by CT scans, at dose level 5 two patients were given more than 20 infusions of Foxy-5 and one of them developed stable disease after 8 weeks, and this patient received continued treatment (51 doses) and still had stable disease after 16 weeks.**
- At each of dose levels 6 and 7, one of three patients received more than 20 doses, i.e. 22 and 21 doses, respectively.**
- At dose level 8 four patients received 20 infusions or more and 2 of these developed stable disease after 8 weeks. One of these two patients only received 28 infusions in total (the patient decided to stop treatment) whereas the other patient received continued treatment (52 doses) and still had stable disease after 16 weeks.**
- All evaluations were made according to CT scans and followed the RECIST criteria.**

Conclusions cont.

- **Based on the results from the phase 1 clinical study with Foxy-5, WntResearch will now conduct a phase 1b clinical study which will continue dose escalation of Foxy-5 with a specific focus on determining the Biological Response Dose (BRD) for Foxy-5, since Foxy-5 impairs cancer cell migration and reduces the formation of distant metastases without inducing tumor regression.**
- **The Biological Response Dose will be determined on the basis of extensive exploration of biomarkers and CT scans.**
- **WntResearch is at the same time preparing for a randomized clinical phase 2 study.**