ANG1005, the first clinical trials:
Preliminary safety and tolerability data in patients with primary and metastatic brain cancers

Danielle Bouchard[1], Betty Lawrence[1], Kelly Elian[1], Wendy Churchill[1], Paula Bento[1], Ann Neale[2], Dimitri Fitsialos[3], Bruno Fraitag[4], Jean-Paul Castaigne[1]

[1]Angiochem Inc., Montreal (Québec), Canada; [2]WinPharm Associates, LLC, Danville, California; [3] Intrinsik Health Sciences Inc., Mississauga (Ontario), Canada; [4] MD, Paris, France

ABSTRACT

Because it prevents the entry of the majority of drugs, the BLOOD-BRAIN BARRIER (BBB) is an obstacle to the clinical treatment of most central nervous system (CNS) diseases. As a result, treatment options for patients with recurrent malignant gliomas or metastatic brain cancer are limited and prognoses are dismal. With their new EPiC platform, Angiochem Inc. is discovering and developing new breakthrough drugs that are uniquely capable of crossing the BBB by receptor-mediated transcytosis. ANG1005, an antimicrotubule chemotherapeutic new chemical entity comprised of the proprietary sequence of amino acids in the EPiC platform conjugated to paclitaxel, is the first of these compounds to reach the clinical stage of development. Preclinical studies have shown that ANG1005 gains entry into the brain compartment by targeting the low-density lipoprotein receptor-related protein (LRP) which is highly expressed on the surface of the BBB. Once inside the brain, ANG1005 enters tumor cells using the same receptor-mediated pathway through LRP, which is upregulated in various cancer cells including malignant glioma and metastatic cancer cells. Paclitaxel is then cleaved by esterase in the lysosomes of the cells where it is able to exert its antimitotic functions. Two (2) multicenter, open-label, dose escalation studies of ANG1005 were initiated in October 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence of efficacy in patients with:

•Recurrent malignant glioma (ANG1005-CLN-01); and
•Advanced solid tumors and/or brain metastases (ANG1005-CLN-02).

The studies use a modified rapid sequential dose escalation design. ANG1005 is administered IV every 21 days with weekly safety visits. Study participants are adult patients with measureable disease and an ECOG performance status less than or equal to 2 who are ineligible for standard treatment options.

As of Feb 20, 2009, data has been gathered from:

•**27** patients with recurrent malignant glioma (18 patients with glioblastoma multiforme, 1 with anaplastic astrocytoma, 7 with anaplastic oligodendroglioma and 1 with oligoastrocytoma; ANG1005-CLN-01); and
•**36** patients with advanced solid tumors (melanoma, n=12; lung cancer, n=8; breast cancer, n=6; hepatocellular carcinoma, n=2; other, n=8) and/or brain metastases (n=26; ANG1005-CLN-02).

Both studies are ongoing and dose escalation is continuing. Safety and tolerability have been good when compared to similar doses of other chemotoxic agents.

New Engineered Peptide Compounds (EPiC) such as ANG1005 represent a potentially safe and effective way to treat currently unmanageable CNS diseases. Results of these studies will determine possible future compounds, doses, and/or indications to be explored in further clinical trials.

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Razelle Kurzrock (ANG1005-CLN-02), *MD Anderson Cancer Center, Houston, Texas*
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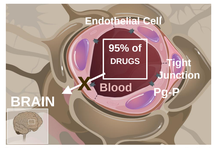
INTRODUCTION

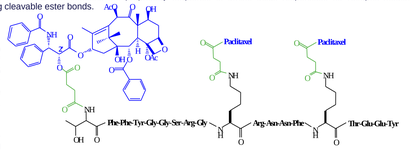


The physical and physiological characteristics that together form the BLOOD-BRAIN BARRIER (BBB) prohibit more than 95% of drugs from reaching the brain, limiting treatment options for patients with brain diseases including primary and metastatic brain cancer. It is vital that approaches be found that allow therapies access to the brain compartment. The scientific community recognizes that the best approaches are ones that use a physiological mechanism. The research presented herein is based on a physiological approach and the observation that most molecules that reach the brain must interact with specific receptors to cross the BBB via active transport.

New Engineered Peptide Compounds (EPiC) discovered and developed by Angiochem Inc. are designed to target the low-density lipoprotein receptor-related protein (LRP), one of a family of receptors expressed at the BBB and upregulated on the surfaces of malignant glioma and metastatic brain cancer cells. This peptide platform is based on formation of new drugs by chemically attaching different molecules to it enabling brain access via transcytosis. ANG1005 is a NCE that contains the proprietary sequence of amino acids responsible for receptor-mediated transcytosis conjugated to paclitaxel using cleavable ester bonds.

Paclitaxel and other chemotherapeutics have limited use in brain cancers due to their inability to penetrate the BBB in sufficient quantities. Preclinical studies show that brain uptake of ANG1005 is ~100x greater than paclitaxel and that once in the brain compartment, ANG1005 favorably targets tumor cells which it enters by endocytosis using the same receptor mechanism. Inside tumor cells, the ester linkages that bind paclitaxel to its peptide backbone are cleaved by esterase, found in high concentration in the lysosomes of the cells. Furthermore, the therapeutic properties of paclitaxel have been shown to be recovered once it dissociates.

Because of strong preclinical data, ANG1005 entered the clinical phase of development in Q4 2007. The present TWO Phase I dose-finding studies represent the first time ANG1005 is being administered to patients with recurrent malignant gliomas (ANG1005-CLN-01), the most common and aggressive primary brain cancers and advanced solid tumors and/or metastatic brain cancer (ANG1005-CLN-02).



ANG1005 (MW=5107) : Angiopep-2 (black) conjugated with 3 paclitaxel molecules (blue); succinyl linkers (green)

MATERIALS and METHODS

Patients with recurrent or progressive malignant glioma (MG; ANG1005-CLN-01) and advanced solid tumors +/- brain metastases (ANG1005-CLN-02) are being recruited into these ongoing, sequential cohort, open-label, dose escalation studies from 9 sites located in the US.

OBJECTIVES

ANG1005-CLN-01

Primary
- To characterize the safety and tolerability of IV administered ANG1005 in patients with recurrent MG
- To identify the maximum tolerated dose (MTD) of ANG1005 in patients with recurrent MG

Secondary
- To examine the pharmacokinetics (PK) of ANG1005
- To confirm the safety and tolerability of ANG1005 at the MTD
- To assess the immunogenicity of ANG1005
- To obtain preliminary information about the antitumor activity of ANG1005 in patients with recurrent MG

ANG1005-CLN-02

Primary
- To characterize the safety and tolerability of IV administered ANG1005 in pts with advanced solid tumors and metastatic brain cancer
- To identify the maximum tolerated dose (MTD) of ANG1005 in pts with advanced solid tumors and metastatic brain cancer

Secondary
- To examine the pharmacokinetics (PK) of ANG1005
- To confirm the safety and tolerability of ANG1005 at the MTD
- To assess the immunogenicity of ANG1005
- To obtain preliminary information about the antitumor activity of ANG1005 in pts w/ advanced solid tumors + metastatic brain cancer

ELIGIBILITY

ANG1005-CLN-01 Inclusion Criteria
- Male and female adults ≥ 18 y.o.
- WHO grades III and IV MG which progressed following resection, first-line treatment or current standard of care
- Measurable disease according to Macdonald
- Ineligible for current standard treatment options
- ECOG performance status score ≤ 2
- Expected survival of at least 3 months

ANG1005-CLN-02 Inclusion Criteria
- Male and female adults ≥ 18 y.o.
- Metastatic / advanced-stage solid tumor that has progressed following standard therapy
- Measurable disease according to RECIST criteria
- Ineligible for current standard treatment options
- ECOG performance status score ≤ 2
- Expected survival of at least 3 months

ANG1005-CLN-01 and ANG1005-CLN-02 EXCLUSION CRITERIA
- Hemoglobin < 9.0 g/dL
- ANC < 1.5 x 10⁹/L
- Platelet count < 100 x 10⁹/L
- Total bilirubin > 1.5 x ULRR
- AST or ALT > 2.5 x ULRR
- Serum calcium > ULRR
- Estimated Cr. clearance < 60 mL/min

TREATMENT AND EVALUATIONS (ANG1005-CLN-01 and ANG1005-CLN-02) :

ANG1005 is currently administered as an IV infusion at a concentration of 1.5 mg/mL and a set rate of 8.0-8.5 mL/min, ***without premedication***.
Treatment is given once q 3 wks until progression, general medical deterioration that warrants discontinuation of treatment or withdrawal of consent.
Patients are closely monitored during the infusion and for up to 24 hrs after the end of infusion with weekly safety visits between treatments.
AEs are collected from the time of the start of the first infusion until 3 wks after the last infusion. The severity of events is assessed according to the NCI CTCAE, v. 3.0, when possible and per protocol otherwise.
Potential neurocognitive changes are being explored through the use of a brief, simple and standardized battery of cognitive performance tests administered before, every 6 wks during, and following treatment.
Blood sampling is being done to look at the PK profile and immunogenicity of ANG1005.
In order to measure disease status, imaging assessments (MRI/CT) are being performed at 6-wk intervals during therapy.

DOSE ESCALATION:
The starting dose will be 30 mg/m².
Dose escalation by dose-doubling will be done for 2 dose levels (i.e. 60 and 120 mg/m²), followed by a modified Fibonacci dose escalation scheme (i.e. dose increases of 67%, 50%, 40% and 33%) thereafter .
Dose escalation will progress until a maximum tolerated dose (MTD) is reached. The MTD is defined as that dose-level at which ≤1 of 6 patients in a cohort develop an emergent dose limiting toxicity (DLT).

Dose Limiting Toxicity (DLT):
- Any Grade 3 or 4 nonhematologic toxicity
- Febrile neutropenia
- Grade 4 neutropenia of ≥ 7 d duration
- Any Grade 4 thrombocytopenia
- Grade 2 peripheral neuropathy > 7 d *OR* a ≥ Grade 3 peripheral neuropathy of any duration

SAFETY RESULTS / PK DATA

ANG1005-CLN-01: Results presented here include data up to and including Feb 20, 2009. **27** patients with recurrent malignant glioma (18 with GLIOBLASTOMA MULTIFORME, 1 with ANAPLASTIC ASTROCYTOMA, 7 with ANAPLASTIC OLIGODENDROGLIOMA, 1 with OLIGOASTROCYTOMA) have received ANG1005 at doses ranging from 30 to 300 mg/m²; escalation is ongoing.

Patient characteristics at study entry (n = 27)

Age (years)	Median	Range	
	55	26-78	
Sex	Male	Female	
	14 (52%)	13 (48%)	
# Prior Chemotherapies	≤ 2	3	≥ 4
	12	5	10
Prior Radiotherapy	Yes	No	
	25	2	
ECOG at Entry	0	1	2
	11 (41%)	13 (48%)	3 (11%)

Safety data are available for all **27** study patients dosed to date; some of the common adverse events seen with chemotherapeutic agents are depicted in the adjacent table.

ANG1005-CLN-02: Results presented here include data up to and including Feb 20, 2009. **36** patients with advanced solid tumors (12 with melanoma, 8 with lung cancer, 6 with breast cancer, 2 with hepatocellular carcinoma and 8 'other' cancers), 26 of which have brain metastases, have received ANG1005 at doses ranging from 30 to 650 mg/m²; escalation is ongoing.

Patient characteristics at study entry (n = 36)

Age (years)	Median	Range		
	54.5	23-76		
Sex	Male	Female		
	18 (50%)	18 (50%)		
# Prior Chemotherapies	≤ 3	4	5	> 5
	13	8	1	14
Prior Radiotherapy	Yes	No		
	25	11		
ECOG at Entry	0	1	2	
	6 (17%)	25 (69%)	5 (14%)	

Safety data are available for all **36** study patients dosed to date ; some of the common adverse events seen with chemotherapeutic agents are depicted in the adjacent table.

Summary of common chemotherapeutic adverse events reported by dose level and CTCAE grade

Dose Level :	30 mg/m²			50 mg/m²			75 mg/m²			105 mg/m²			200 mg/m²			300 mg/m²		
# Patients :	3 pts			6 pts			3 pts			6 pts			4 pts			5 pts		
Total # Cycles/Cohort :	7 cycles			10 cycles			8 cycles			14 cycles			9 cycles			7 cycles		
CTCAE Grade :	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Leucopenia	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Anemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infusion Related Rxn	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Peripheral Neuropathy[1]	0	0	0	0	0	0	0	0	0	0	1[2]	0	0	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Myalgia / Arthralgia[1]	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

n = number of patients that experienced an event, whether or not deemed relater to study drug
[1] Parameter not included in CTCAE; severity assessed *per protocol*: Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening
[2] Verbatim term = Stiffness of extremities

Summary of common chemotherapeutic adverse events reported by dose level and CTCAE grade

Dose Level :	30 mg/m²			60 mg/m²			120 mg/m²			200 mg/m²			300 mg/m²			420 mg/m²			500 mg/m²			550 mg/m²			650 mg/m²		
# Patients :	1 pt			3 pts			3 pts			3 pts			7 pts			6 pts			4 pts			3 pts			6 pts		
Total # Cycles/Cohort :	6 cycles			9 cycles			10 cycles			12 cycles			13 cycles			14 cycles			4 cycles			8 cycles			11 cycles		
CTCAE Grade :	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Leucopenia	0	0	0	0	1	0	0	0	0	2	0	0	2	1	1[2]	2	2	0	0	1	0	2	0	1	0	5	1
Neutropenia	0	0	0	1	0	0	0	0	0	2	0	0	1	0	1[2]	4	0	0	1	0	0	1	0	1	0	2	5
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[2]	0	0	1	0	0	0	0	1	0	1	1	0
Anemia	0	0	0	1	0	0	0	0	0	1	0	0	2	1	0	1	0	0	4	0	0	2	0	0	2	2	0
Infusion–Type Rxn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0
Peripheral Neuropathy[1]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Myalgia / Arthralgia[1]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

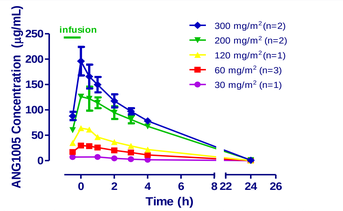
n = number of patients who experienced an event, whether or not deemed related to study drug
[1] Parameter not included in CTCAE; severity assessed *per protocol*: Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening
[2] This patient developed grade 4 leucopenia, neutropenia and thrombocytopenia and grade 2 anemia; the patient was heavily exposed to radiation prior to inclusion

Neurocognitive Data: Data to date show that ANG1005 does not affect cognitive performance at these doses in these populations; the ANG1005-CLN-02 patient who has maintained stable disease for 20.4 wks, and is currently ongoing ,significantly improved from baseline to 6 wks (Cycle 2) on memory, processing speed and executive function, and maintained that improvement at the 12 wk (Cycle 4) assessment (18-wk data unavailable at this time).

Immunogenicity Data: Data from **31** patients measured to data indicate that ANG1005 does not elicit an immune response.

Pharmacokinetic Data: PK data presented here are *preliminary* results obtained from cycle 1 in **9** patients dosed between 30 and 300 mg/m²; data obtained so far show linear bioavailability of ANG1005.

Parameter	Value / Range (as applicable)				
Dose (mg/m²)	30	60	120	200	300
n	1	3	1	2	2
C_{max} (ug/mL)	13	27-32	64	128-146	168-224
T_{max} (h)	1	1.0-1.5	1	1.0-1.5	1
AUC_{inf} (ug·h/mL)	34	137-145	281	1061-1163	909-1459
half-life (h)	1.5	2.4-2.7	2.8	3.5-3.7	3.1-3.6
CL (mL/m²·h)	888	414-438	428	172-189	206-330
Vd (mL/m²)	1924	1459-1714	1743	864-1004	918-1694



Note that all values < the lower limit of quantification (0.5 µg/mL) have been reported as 0.0

TUMOR RESULTS

TUMOR RESPONSE DATA : 6-week tumor response data is available for **20** patients. Although efficacy is not expected at the low doses used thus far, 6-week data reveal 2 minor responses (~10% decrease at 30 and 105 mg/m²).

	30 mg/m² n = 2	50 mg/m² n = 4	75 mg/m² n = 3	105 mg/m² n = 5	200 mg/m² n = 4	300 mg/m² n = 2
SD at 6 wks	1	0	1	2	1[1]	1[1]
SD > 6 wks	0	0	0	0	1[2]	
SD at 12 wks	0	0	0	0		
PD at 6 wks	1	4	2	3	2	1
PD at 12 wks	1	0	1	2		

PR = Partial Response; SD = Stable Disease; PD = Progressive Disease
1 Patient ongoing; 2 Patient withdrawn prior to progression

TUMOR RESPONSE DATA : Tumor response data are available for **21** patients to date. PR was observed in 1 endometrial Ca patient w/ lung, liver and brain metastases dosed at 650 mg/m². One patient dosed at 420 mg/m² had SD at 18 wks and is ongoing.

	30 mg/m² n = 1	60 mg/m² n = 2	120 mg/m² n = 3	200 mg/m² n = 3	300 mg/m² n = 4	420 mg/m² n = 5	550 mg/m² n = 1	650 mg/m² n = 2
PR > 6 wks	0	0	0	0	0	0	0	1[1]
SD at 6 wks	1	1	1	2	0	0	0	
SD > 6 wks	0	0	0	0	0	1[2]	0	
SD at 12 wks	1	1	1	1	0	0	0	
SD > 12 wks	0	0	0	0	0	0	1[2]	
SD at 18 wks	0	0	0	0	0	0	0	
SD > 18 wks	0	0	0	0	0	1[1]	0	
PD at 6 wks	0	1	2	1	4	3	0	1
PD at 12 wks	0	0	0	1	0	0	0	
PD at 18 wks	1	1	1	1	0	0	0	

CONCLUSIONS

- **ANG1005 has an excellent safety and tolerability profile, as evidenced by laboratory and neurocognitive data, at doses tested to date in patients with recurrent MG and advanced solid tumors and brain mets**
- **ANG1005 does not show evidence of eliciting an immune response in humans**
- **PK data analyzed to date show a linear bioavailability of ANG1005**
- **Data to support clinical efficacy of ANG1005 has begun being gathered at higher doses in patients with advanced solid tumors and brain mets**