2. STUDY SYNOPSIS

Name of Sponsor: Facet Biotech Corporation (North America) Biogen Idec Inc./Biogen Idec Ltd. (Rest of World) **Company Conducting Study:** Biogen Idec Inc./Biogen Idec Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Volociximab (M200)	**Name of Active Ingredient:** Volociximab (M200)	

Title of Study:

A Phase 1/2, Open-Label, Adaptive, Randomized Study of Liposomal Doxorubicin With or Without M200 (Volociximab) for the Treatment of Subjects With Advanced Epithelial Ovarian Cancer or Primary Peritoneal Cancer That Have Relapsed After Prior Therapy With a Platinum/Taxane-Based Chemotherapy

Principal Investigator:

[redacted]
Belgium

Study Period: Date of first treatment: 26 July 2007 Date of early study termination: 28 August 2008	**Phase of Development:** 1/2

Phase 1b Study Objectives:

Primary objective:

- To evaluate the safety and tolerability of volociximab in combination with liposomal doxorubicin.

Secondary objective:

- To evaluate the PK of volociximab in combination with liposomal doxorubicin.

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Phase 2 Study Objectives:

Primary objectives:

- To evaluate the efficacy of volociximab in combination with liposomal doxorubicin in advanced epithelial ovarian cancer or primary peritoneal cancer.
- To evaluate the safety and tolerability of volociximab in combination with liposomal doxorubicin.

Secondary objectives:

- To evaluate the pharmacokinetics (PK) of volociximab in combination with liposomal doxorubicin.
- To evaluate quality of life (QoL) benefits of volociximab in combination with liposomal doxorubicin.

Additional objectives:

- To evaluate the pharmacodynamic activity of volociximab through studies of serum protein biomarkers.
- To investigate the potential relationship between tumor expression of $\alpha 5\beta 1$ or other relevant biomarkers and clinical response to volociximab.
- To measure volociximab and possibly other protein biomarkers in ascitic fluid obtained from subjects in whom paracentesis can be safely performed and to investigate potential correlations with clinical response to volociximab.

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Methodology:

This study was a Phase 1/2, global study in subjects with advanced epithelial ovarian cancer or primary peritoneal cancer that had relapsed after prior therapy with a platinum/taxane-based chemotherapy.

Phase 1 was a "3+3" design to evaluate the safety and tolerability of different doses and/or regimens of volociximab in combination with a fixed dose and schedule of liposomal doxorubicin (40 mg/m^2 once every 4 weeks [q4wk]) to determine the recommended Phase 2 dose. Phase 2 was a parallel, 3-arm adaptive randomization phase to compare the efficacy and safety of liposomal doxorubicin plus volociximab with liposomal doxorubicin alone.

Each treatment course was to consist of two 4-week treatment cycles of liposomal doxorubicin alone or in combination with volociximab. Disease response was to be assessed at Week 8 (Day 50 to 57) and every 8 weeks thereafter during the treatment period. Subjects who achieved stable disease or better per the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0) were eligible to continue receiving volociximab at the same dose and schedule until disease progression or unacceptable toxicity occurred. There was no limit to the number of doses of volociximab a subject could receive. The maximum number of doses of liposomal doxorubicin a subject could receive was 12 (i.e., through Treatment Course 6).

Despite no protocol defined stopping criteria being met, on 28 August 2008, enrollment in the study was terminated after a planned interim evaluation of preliminary efficacy data indicated that there was no clinically or statistically significant difference in progression-free survival (PFS) between the 3 treatment groups in the Phase 2 portion of the study. This decision was made by Biogen Idec and Facet and supported by an Independent Data Monitoring Committee.

Number of Subjects (Planned and Analyzed):

Planned: The minimum planned sample size was 51 (6 in Phase 1 and 45 in Phase 2). The maximum planned sample size was to be capped at 174 (24 in Phase 1 and 150 in Phase 2). The study was to be conducted at approximately 50 study sites in North America and the Rest of World.

Analyzed: A total of 138 subjects were enrolled at 39 global study sites: 10 subjects in the Phase 1 portion of the study and 128 subjects in the Phase 2 portion of the study.

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Study Population:

Inclusion criteria:

1. Must have given written informed consent and any authorizations required by local law (e.g., Protected Health Information).
2. Females aged ≥18 years old at the time of informed consent.
3. Advanced (Stage III or IV) histologically documented epithelial ovarian cancer or primary peritoneal cancer (excluding small, round-cell histologies).
4. Recurrent or persistent disease.
5. Received no more than 2 prior cancer treatment regimens, at least one of which must have included a platinum/taxane based therapy (carboplatinum, cisplatinum, or another organoplatinum compound). If the same regimen is given more than once, it will only count as one regimen. Similarly, if components of a regimen are given more than once using the same schedule, it will only count as one regimen.
6. Have measurable disease, per RECIST, or evaluable disease (i.e., non target lesions only) **[Phase 1b only]**
7. At least 1 target lesion to assess response by RECIST criteria. (Tumors within a previously irradiated field were designated as non-target.) **[Phase 2 only]**
8. ECOG Performance Status ≤1.
9. Life expectancy >12 weeks.
10. Available paraffin block or unstained paraffin sections on glass slides containing representative tumor tissue from the most recent tumor biopsy/resection. **[Phase 2 only]**
11. Subjects of child bearing potential must have been willing to practice effective contraception during the study and be willing and able to continue contraception for at least 6 months after their last dose of study treatment (about 5 half lives).

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Exclusion criteria:

1. Clinical laboratory values greater than or less than the following laboratory thresholds:
    - Granulocyte count <1500/μL
    - Platelet count <75,000/μL
    - Hemoglobin <8.5 g/dL (hemoglobin may be supported by transfusion or erythropoietin or other approved hematopoietic growth factors; darbepoetin [Aranesp®] is permitted)
    - Serum bilirubin >2.0 × upper limits of normal (ULN)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5 × ULN (AST and ALT >5 × ULN for subjects with liver metastasis)
    - Serum creatinine >2.0 mg/dL
    - International normalized ratio >1.5
    - Activated partial thromboplastin time >1.5 × ULN
2. Unstable angina or a history of myocardial infarction within 6 months prior to Day 1.
3. New York Heart Association ≥Grade II congestive heart failure.
4. Subjects who had received prior (liposomal) anthracycline or anthracenedione therapy.
5. Any investigational, anti-cancer therapy within 6 weeks prior to Day 1.
6. Any non-investigational, anti-cancer therapy within 4 weeks prior to Day 1.
7. Prior treatment with anti-angiogenic agents.
8. Subjects who were taking concomitant immunomodulatory agents including, but not limited to, interferons, interleukins, systemic steroids, cyclosporine, tacrolimus, calcineurin inhibitors, chronic low-dose methotrexate, or azathioprine. (The use of inhaled or intranasal steroids or oral steroids at a dose of ≤10 mg/day prednisone or its equivalent are permitted.)
9. Subjects who required treatment with an anti-coagulant with the exception of low-dose Aspirin® (≤81 mg/day), warfarin (≤1 mg/day), or heparin for intravenous (IV) catheter patency.
10. Subjects with a left ventricular ejection fraction <50%.

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Exclusion criteria (continued):

11. History of stroke or transient ischemic attack within 6 months prior to Day 1.
12. Clinically significant peripheral vascular disease.
13. Evidence of bleeding diathesis or coagulopathy. (Note: Prior history of deep vein thrombosis will not exclude subjects from participating in this study.)
14. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to Day 1.
15. Serious, non-healing wound, ulcer, or bone fracture.
16. Evidence of autoimmune disease including, but not limited to, ulcerative colitis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and other disease in which immune function or immune competence was known to be impaired.
17. Active infection requiring systemic antibiotics, antivirals, or antifungals including HIV/AIDS, hepatitis B, or hepatitis C infection.
18. Any history of lymphoproliferative disorder.
19. Known human anti-murine antibody and/or human anti-chimeric antibody.
20. Known central nervous system or brain metastases.
21. History of other malignancies within 3 years of Day 1, except for adequately treated carcinoma in situ of the cervix, ductal carcinoma in situ of breast, or basal, or squamous cell skin cancer.
22. Pregnant (positive pregnancy test) or lactating.
23. Inability to comply with study and follow-up procedures.
24. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that in the opinion of the Investigator gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications.

Study Treatment, Dose, Mode of Administration, Batch Numbers:

Volociximab (7.5 and 15 mg/kg) was administered by IV infusion. Eight lots of volociximab were used during the study: Lots [redacted]

Liposomal doxorubicin (40 mg/m^2) was administered by IV infusion. Commercially available liposomal doxorubicin was used in this study.

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Duration of Treatment and Follow-Up:

The study period consisted of screening, treatment, and long term follow-up.

Screening:

Screening procedures to evaluate subject eligibility for the study were to be initiated within 28 days prior to administration of the first dose of study treatment (i.e., Study Day 1). All subjects who met the eligibility criteria were to be registered within 4 days prior to Study Day 1.

Treatment Period:

Subjects were to report to the study site to receive study treatment. Each treatment course was to consist of 2 cycles of liposomal doxorubicin (40 mg/m^2 q4wk) alone or in combination with volociximab. The dose and schedule of volociximab were dependent on the emerging toxicity data. A follow-up disease assessment visit was to be performed at Week 8 (Study Day 50 to 57). Subjects who did not have progressive disease at this visit were eligible to continue receiving study treatment until disease progression or unacceptable toxicity occurred.

When subjects discontinued study treatment, they were to return to the study site for a single, follow-up visit at least 4 weeks after their last infusion of study treatment and complete End of Treatment Visit procedures and evaluations.

Long-Term Follow-Up:

After the End of Treatment Visit, subjects were to be entered into long-term follow-up, where they were to be followed by verbal or written contact every 3 months for the first year and every 6 months thereafter for continuation of response (if applicable), disease progression, first subsequent cancer therapy, survival, and adverse events (AEs), with particular emphasis on neurological signs or symptoms. Long-term follow-up was to continue until the subject died, became lost to follow-up, or withdrew informed consent.

Enrollment in the study was terminated early on 28 August 2008 after a planned interim evaluation of preliminary PFS data indicated that there was no statistical difference in the median PFS between treatment groups in the Phase 2 portion of the study.

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Criteria for Evaluation:

Safety: Safety evaluations included physical examinations; vital sign measurements; AE and serious adverse event (SAE) recording; hematology and blood chemistry analyses; urinalysis, electrocardiogram, and left ventricular ejection fraction (LVEF) evaluations; and measurement of anti-volociximab antibody formation. The severity of each AE was assessed by the Investigator using the adult National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0). In this study, the relationship of each AE to study treatment was classified by the Investigator as unrelated, unlikely related, possibly related, or related to study treatment. "Related AEs" were considered to be unlikely related, possibly related, or related to study treatment.

Efficacy: Disease response was evaluated using RECIST. The primary efficacy endpoint in Phase 2 was PFS, defined as the time from randomization to tumor progression (using the Investigator's assessment) or death by any cause. Secondary efficacy endpoints included time-to-progression, objective response rate, overall survival, duration of response, and CA-125 response.

Pharmacokinetics: Serum concentrations of volociximab and plasma concentrations of liposomal doxorubicin were measured throughout the study. These measurements were to be used to estimate PK parameters.

Quality of Life: QoL assessments were performed using FACT-O (Version 4.0) and EQ-5D (EuroQoL) questionnaires.

Pharmacodynamics: Exploratory pharmacodynamic endpoints were to include the following:

- Analysis of serum protein biomarkers.
- Analysis of tumor expression of $\alpha 5\beta 1$ or other relevant biomarkers.
- Analysis of volociximab and possibly other protein biomarkers in ascitic fluid.

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Statistical Methods:

Demographics and baseline characteristics: All demographic and baseline disease characteristic analyses were performed on the Full Analysis Population, defined as all subjects who received any part of an infusion of study treatment (Phase 1) or all subjects who were randomized and received any part of an infusion of study treatment (Phase 2). Continuous variables were summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum), while categorical variables were summarized using frequencies and percentages (n, %).

Subject Disposition: Subject disposition analysis was performed on the Enrolled Population. The number and percentage of subjects dosed and those who discontinued study treatment were summarized. The number of subjects enrolled by study site was summarized.

Safety: Safety analyses were performed on the Safety Population, defined as all subjects who received any part of an infusion of study treatment. The incidence of AEs was summarized by system organ class, preferred term, and toxicity grade. Overall AEs, related AEs, SAEs, and deaths were listed by subject. Subject listings for clinical laboratory parameters, vital signs measurements, physical examination findings, urinalysis results, anti-volociximab antibody formation were provided. Shift tables for clinical laboratory parameters were created.

Efficacy: The primary efficacy endpoint (PFS) was performed on the Full Analysis Population in Phase 2, defined as all subjects who received any part of an infusion of study treatment. PFS was analyzed using both Kaplan-Meier and Cox proportional hazard methodology. Subjects not experiencing a PFS event were censored at the date of last visit with adequate assessment or study termination (End of Treatment visit), whichever was earlier.

Pharmacokinetics: PK analyses were performed on data from the PK Population, defined as all enrolled subjects who received any part of an infusion of study treatment and had at least 1 sample collected for PK analysis. There were insufficient sample collection timepoints in the study for evaluating the PK parameters; therefore, only peak and trough results were analyzed.

Quality of Life: Since the primary efficacy endpoint was not met, QoL analyses were not performed.

Pharmacodynamics: Since the primary efficacy endpoint was not met, exploratory analyses were not performed.

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Results:

Subject disposition:

- 138 subjects were enrolled at 39 global study sites.
- Of the 10 subjects enrolled in Phase 1, 9 received study treatment: 3 in Cohort 1 (liposomal doxorubicin + 7.5 mg/kg of volociximab once a week [qwk]) and 6 in Cohort 2 (liposomal doxorubicin + 15 mg/kg of volociximab qwk).
- Of the 128 subjects enrolled in Phase 2, 127 received study treatment: 66 in Group A (liposomal doxorubicin alone), 34 in Group B (liposomal doxorubicin + 15 mg/kg of volociximab once every 2 weeks [q2wk]), and 27 in Group C (liposomal doxorubicin + 15 mg/kg of volociximab qwk).
- No subject remained on study at the time of database lock.

Demographics and baseline disease characteristics:

- The majority of all subjects (>98%) were White females.
- The median age was 62 years (Phase 1) and 57 years (Phase 2).
- All 9 subjects (100%) in Phase 1 and 114 subjects (90%) in Phase 2 had epithelial ovarian cancer. Thirteen subjects (10%) in Phase 2 had primary peritoneal cancer.
- All subjects had Stage III or IV disease.
- The median number of prior cancer regimens was 2.
- Five subjects in Phase 1 had platinum-resistant disease, 3 had platinum-sensitive disease, and 1 had platinum-refractory disease. Fifty-six subjects (44%) in Phase 2 had platinum-resistant disease, 51 (40%) had platinum-sensitive disease, and 20 (16%) had platinum-refractory disease.

Efficacy:

- Enrollment in the study was terminated on 28 August 2008 after a planned interim evaluation of preliminary efficacy data indicated that there was no clinically or statistically significant difference in PFS between the 3 treatment groups in the Phase 2 portion of the study.
- The Kaplan-Meier estimates of the median PFS for Groups A, B, and C were 173 (95% confidence interval [CI]: 112 to 254), 123 (CI: 63 to 366), and 221 (CI: 70 to 326) days, respectively. The median follow-up was 236 days (7.8 months).

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Results:

Safety:

Phase 1

- No dose-limiting toxicities (DLTs) were reported in Phase 1; therefore, 15 mg/kg was chosen as the volociximab dose for the Phase 2 portion of this study.
- One safety finding was the incidence of Grade 3 palmar-plantar erythrodysaethesia syndrome in 3 subjects (33%), which was thought to be possibly higher than the incidence reported for 40 mg/m^2 liposomal doxorubicin alone q4wk (between 0 and 8%) [Campos et al. 2001; Markman et al. 2000; Rose et al. 2001]. This finding raised concerns that volociximab could be exacerbating this liposomal doxorubicin-related event. An evaluation of plasma concentrations of liposomal doxorubicin in all 3 of these subjects did not reveal higher plasma concentrations than expected [Doxil® 2008]; however, subjects were to be closely monitored for palmar plantar erythrodysaethesia syndrome during the Phase 2 portion of the study.

Safety:

Phase 2

- There did not appear to be any clinically meaningful changes in the safety profile between the control group (Group A; liposomal doxorubicin alone) and the experimental treatment groups (Groups B and C; liposomal doxorubicin + volociximab).
- The most common (≥25% in any treatment group) AEs regardless of causality were anemia, neutropenia, nausea, abdominal pain, constipation, vomiting, stomatitis, palmar-plantar erythrodysaethesia syndrome, fatigue, asthenia, and peripheral edema.
- The most common (≥25%) volociximab-related AEs were nausea, vomiting, and fatigue.
- Forty-one (32%) subjects experienced at least 1 SAE. The most common SAEs in all treatment groups were disease progression and intestinal obstruction.
- Two deaths occurred during the treatment period (1 in Group A and 1 in Group C), and 48 deaths occurred during the long-term follow-up period. One of the 2 deaths that occurred during the treatment period was as a result of intoxication and was not considered related to study treatment. The other death was from unknown causes, and was considered unlikely related to study treatment.

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Results (continued):

Safety:

Phase 2

- Overall the incidence of palmar-plantar erythrodysaethesia syndrome appeared similar between treatment groups. Thirty-seven subjects developed palmar-plantar erythrodysaethesia syndrome: 20 subjects (30%) in Group A, 10 (29%) in Group B, and 7 (26%) in Group C. Eight subjects developed Grade 3 palmar-plantar erythrodysaethesia syndrome: 5 (8%) in Group A; 2 (6%) in Group B, and 1 (4%) in Group C. No subjects developed palmar-plantar erythrodysaethesia syndrome ≥Grade 4. Thus, the concerns raised by the data in the Phase 1 portion of the study were not borne out in Phase 2.
- Evaluation of AEs associated with other anti-angiogenic drugs (thromboembolic events, hemorrhagic events, hypertension, proteinuria, and AEs occurring during or within 24 hours after a volociximab infusion) and AEs associated with other anti-integrins (progressive multifocal leukoencephalopathy and neurological events) revealed no safety issues of clinical concern with 15 mg/kg volociximab infused qwk or q2k in this study.
- Evaluation of vital sign measurements, physical examination findings, hematology, blood chemistry, urinalysis, electrocardiogram, LVEF, and immunogenicity revealed no safety issues of clinical concern.

Pharmacokinetics:

- Serum concentrations of volociximab accumulated after the first infusion with trough concentrations continuing to increase through the 4th dose of Cycle 1 for Phase 1 and 2.
- As expected, the pre-dose concentrations of liposomal doxorubicin were very low compared with the 10-minutes post-infusion concentration on Day 29. Additionally, there was no trend towards a change in concentration over time, suggesting that volociximab did not change doxorubicin concentrations.

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Conclusions:

- Volociximab appeared to be tolerated when administered by IV infusion up to 15 mg/kg qwk in combination with liposomal doxorubicin in subjects with advanced epithelial ovarian cancer or primary peritoneal cancer that had relapsed after prior therapy with a platinum/taxane-based chemotherapy.
- The addition of volociximab did not appear to increase the toxicity profile of liposomal doxorubicin. The safety profile of the combination was as expected for a myelosuppressive chemotherapeutic (liposomal doxorubicin). Safety findings observed with other anti-angiogenic agents (e.g., bevacizumab), such as thromboembolic events, were observed, but the small sample size precludes accurate comparison of the propensity of the 2 classes of drugs to induce such effects.
- Preliminary efficacy data indicated that there was no clinically or statistically significant difference in PFS between the 3 treatment groups. Therefore, study enrollment was terminated early.
- The PK data indicated that all volociximab dosing regimens in Phase 1 and Phase 2 provided volociximab concentrations greater than the targeted pre-clinical efficacy levels (150,000 ng/mL). Additionally, there was no clear evidence that volociximab altered liposomal doxorubicin concentrations.

Publications Based on the Study:

Antonella P, Sessa C, Delmonte A et al. Interim results from a Phase 1/2 study of volociximab in combination with liposomal doxorubicin in patients with advanced epithelial ovarian or primary peritoneal carcinoma that relapsed after platinum/taxane chemotherapy. European Journal of Cancer 2008; 20th EORTC–NCI–AACR:Abstract #512

Vergote I, Colombo N, Kutarska E et al. Phase 2 study comparing volociximab (an anti-angiogenic antibody) and pegylated liposomal doxorubicin (PLD) with PLD alone in recurrent ovarian or primary peritoneal cancer. American Society of Clinical Oncology 2008

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