

Kentucky Intraputamenal GDNF Phase I Clinical Trial

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Disclosures: None to declare

UK GDNF/Liatermin® Trial

Timeline

- **1993 – 97** GDNF discovered and cloned; Liatermin produced in *E. coli*, shown to help in animal models of PD
- **01/01 – 1st** protocol prepared at UKMC for intraputamenally-delivered GDNF, guided by:
 - ◆ preclinical studies at UKMC in monkeys
 - ◆ side-effect profile of Phase 1/2 ICV study
 - ◆ development of a suitable delivery system (Medtronic Pump)

- 11/01 – UKMC develops alternative funding and submits investigator-initiated IND to the FDA after Amgen declines to underwrite the study
- 03/02 – IRB approval to begin recruitment
- 05/02 – 1st patient enters UKMC study
- 06/02 – Amgen asks to assume sponsorship

University of Kentucky - Phase I FDA-Approved Dose-Escalation Open Label Trial

- ◆ Phase I: dosing, tolerability and safety study
- ◆ 10 PD patients, H&Y stage 3-4 in “off” state, daily “on/off”, symptomatic tx stable x 2 mo
- ◆ Chronic unilateral intraputamenal Infusion of GDNF: 3 → 10 → 30 $\mu\text{g}/\text{day}$ q 8 wks
- ◆ Primary objective: Assessment of safety
- ◆ Secondary objective:
 - ◆ Efficacy (UPDRS, H&Y, CAPSIT, S&E, MMSE, med Δ and Personal diaries)
 - ◆ Device performance

Summary

- Treatment safe and well tolerated by the 10 subjects at all delivered doses
- Significant indications of bilateral efficacy
 - ◆ Animal studies indicate convection enhanced delivery (CED) into internal capsule white matter tracts distributes drug bilaterally

GDNF Extended Treatment, 1 and 5-year Withdrawal UPDRS Scores

Tests	Base	1-year of Treatment	End of Treatment	1 year later	5 years later
UPDRS OFF	64 ± 5	37 ± 3 (-42%)	44 ± 3 (-31%)	63±3 (0%)	
UPDRS ON	47 ± 3	29 ± 3 (-38%)	30 ± 3 (-36%)	43±3 (-0.1%)	
UPDRS III OFF	40 ± 4	22 ± 2 (-45%)	26 ± 3 (-35%)	39±3 (0%)	49±7 (+23%)
UPDRS III ON	23 ± 2	14 ± 3 (-39%)	13 ± 3 (-43%)	19±3 (-17%)	31±7 (+35%)

- **01/03 – Multicenter Phase 2 study begins recruitment, human ICV phase 1/2 “negative” study published**
- **04/03 – Bristol “positive” study published**
- **06/04 – Phase 2 study “unblinded”; GDNF appears to lack efficacy**
- **08/04 – Draft report of animal toxicity study submitted to Amgen; antibodies reported in 2 patients, more to come**

- **09/04 – All investigators ordered to stop administering Liatermin® to patients.**
- **10/04 – Fox Foundation “summit” meeting**
- **11/04 – Amgen/Investigator meeting to review data**
- **12/04 – Draft copy of publication for Phase 2 study circulated**
- **01/05 – Amgen and UKMC investigators meet with FDA representatives**

Differences Among Clinical Trials

- Three different catheters were used in the three trials
 - ◆ Medtronic single-port: Phase 2
 - ◆ Gill single-port: Bristol study
 - ◆ Medtronic multi-port: Kentucky Phase 1 study
- Two different delivery sequences were used
 - ◆ Bristol Study and Phase 2 used simple continuous infusion
 - ◆ Kentucky Study used complex-continuous (pulsatile/convection enhanced) delivery

- **06/05 – Federal court in New York rules patients “failed to demonstrate a ‘clear and unambiguous’ promise” [of access to drug by Amgen] and “signed consent documents that acknowledged Amgen’s right to terminate the research trials.”**

A point of Contract Law

- **08/05 – Federal Court in the Eastern District of Kentucky delivers verdict similar to New York**
- **05/08 – Nelson, N. Monkey in the Middle: How one drug company kept a Parkinson’s disease breakthrough out of reach . BookSurge Publishing, May 2008.**

■ The GDNF dispute illustrates the urgent need for pharmaceutical companies, clinical researchers, and patients to join forces in modifying medical research in which study participants are commonly treated as passive subjects, have no control on the research process, and are often misled by the expectation of a therapeutic outcome.

Leading Edge: The hard way to a bill of rights. The Lancet Neurology 4:787, 2005

The hard way to a Bill of Rights

Respect, beneficence, and justice were established as ethical principles governing human medical research in the USA by The Belmont Report over 25 years ago. These principles are met when research participants are fully informed and are treated with compassion, care, and equity. Currently, a group of US patients with Parkinson's disease and their neurologists might doubt that clinical trials are guided by any of these principles.

In September 2004, Amgen stopped a trial of intraputamin glial-cell-derived neurotrophic factor (GDNF) for the treatment of advanced Parkinson's disease because of concerns about safety and efficacy. Several patients, who claim physical and quality-of-life benefits of GDNF, their physicians, and supporting advocacy groups, are now involved in a battle against the company's decision. Exceptionally, in a society in which pharmaceutical companies are often blamed for not paying sufficient attention to safety, these patients want to continue their treatments and are suing Amgen to regain access to GDNF, for which the company holds patent rights. Courts in New York and Kentucky ruled in favour of Amgen, recognising the legal right of the company to terminate the trial. The Court of Appeals will hear the patients' arguments in December.

On the basis of evidence from animal studies of the restorative properties of GDNF on dopaminergic neurons and two positive independent phase I trials in the UK and the USA, Amgen initiated a phase II study in 2003. The company ended the trial, claiming that it failed to meet their primary endpoints and attributing any benefits of the drug to the placebo effect; simultaneously, a study of GDNF in monkeys showed acute toxic effects in several animals, adding a safety reason for Amgen to discontinue the treatment. The trial data are expected to be published soon, at which time the scientific community will be able to judge the sensibility of Amgen's resolution. Several of the principal investigators involved in the trial, however, have publicly refuted Amgen on scientific grounds, convinced that the trial suggests efficacy of GDNF. These investigators support the patients' plea for compassionate treatment. They believe Amgen's decision was taken under the pervasive psychological effect of the *Vioxx* crisis, and as a consequence of the company's overestimation of the risks from the toxicology studies in monkeys.

Amgen should be praised for taking a prudent decision, in so far as it is rooted in scientific evidence and ethical reasoning. However, the company will gain further respect from the medical and patient communities by reanalysing their data. To date, over a 100 patients with Parkinson's disease have been treated with GDNF without major adverse effects. Even if, once they are published, the phase II trial data convince investigators of the drug's lack of efficacy, there are still important methodological issues worth exploration. For example, the design of the intraputamin catheter system used to deliver GDNF in these patients was different to that used in the positive phase I UK study.

If Amgen sticks to its decision not to initiate a new study, this should not prevent the company from reconsidering the provision of GDNF on a case-by-case basis, allowing the compassionate treatment of those with exceptional needs who have participated in former trials. The case highlights the ethical complications introduced by the documents that legally give power to a sponsor over the direction of a study despite, as in this case, the opinion of some of the academic principal investigators.

The GDNF dispute illustrates the urgent need for pharmaceutical companies, clinical researchers, and patients to join forces in modifying medical research in which study participants are commonly treated as passive subjects, have no control on the research process, and are often misled by the expectation of a therapeutic outcome. It is ethically undesirable that participants should not be engaged about the primary intention of a clinical trial, which is usually to test a drug rather than deliver a therapy. Parkinson's disease advocacy groups in the USA are setting a remarkable example by working towards a Research Participant's Bill of Rights that would entitle them to be better informed and make decisions according to their own appraisal.

The patients in this case were willing to accept any risks when they agreed to participate in Amgen's study. However, none of them anticipated that those risks would include the termination of a potentially beneficial treatment, leaving them with no alternative therapy. It is understandable that these patients now ask for the respect, beneficence, and justice that should guide clinical research. ■ The Lancet Neurology

The Belmont Report
<http://www.fda.gov/guidelines/belmont.html>

What factors might have been considered in deciding not to include a sham neurosurgical arm?

- The study was designed in 2001 as a Phase I clinical trial to help establish dose and to evaluate safety and tolerance
- It was decided at that time that a sham control was not appropriate for a Phase I study

What were the ethical considerations, and how did these impact the study design?

- **Subjecting patients to an untested surgical procedure:** select more severely effected subjects who are no longer managed adequately with symptomatic medications
- **Allowing patients an alternative to Deep Brain Stimulation surgery:** enroll subjects meeting criteria who would choose participation over DBS surgery

Are there questions that can't be answered without use of a sham neurosurgical arm?

- Placebo effect

- ◆ Duration?

- ◆ Consistent?

- ◆ Physiologically related?

- Investigator bias

- Systematic procedural errors

If there are discordant results from trials with and without a sham neurosurgical arm, how do you assess the results?

■ Compare studies

- ◆ If it can be presumed that a 1st study without a sham arm is sufficiently similar to a 2nd study with, then one can subtract sham arm results of the 2nd from the experimental results of the 1st, assuming no Type 2 errors in the 2nd study (2nd study viewed as historical control).
- ◆ Apply the method to several studies as a quasi meta-analysis

■ Design a random start study when possible

- ◆ UK GDNF study could have been staggered in a double-blinded fashion
 - ◆ All subjects undergo surgery, GDNF treatment and washout
 - ◆ Subjects receive vehicle for variable times before receiving GDNF
 - ◆ Data put in register at time of analysis
- ◆ Longer trial duration, more costly