Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Silver Spring, 8777 Georgia Avenue, Silver Spring, Maryland

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting for September 9, 2005

On September 9, 2005, the committee discussed new drug application (NDA) 21-865, proposed trade name Pargluva (muraglitazar) Tablets, 2.5 milligrams (mg) and 5 mg, Bristol-Myers Squibb, for the treatment of type II diabetes mellitus.

These summary minutes for the September 9, 2005 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on September 13, 2005.

I certify that I attended the September 9, 2005 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____//S//_____
Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

_____//S//_____
Nelson B. Watts, M.D.
Chair

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
September 9, 2005
NDA 21-865 Pargluva™ (muraglitazar)
FINAL MINUTES

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 9, 2005, at the Holiday Inn, located at 8777 Georgia Avenue, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors.

The meeting was called to order by Nelson Watts, M.D., Chair; the conflict of interest statement was read into the record by Cathy Groupe (Executive Secretary). Opening remarks were made by David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products. There were approximately 275 persons in attendance. There was one speaker for the Open Public Hearing session.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (voting)
Nelson B. Watts, M.D. (Chair); Dean A. Follmann, Ph.D; Paul D. Woolf, M.D.; Sonia Caprio, M.D.; Steven W. Ryder, M.D. (Industry Representative)

Endocrinologic and Metabolic Drugs Advisory Committee Consultants (voting):
Kenneth D. Burman, M.D.; Lynne L. Levitsky, M.D.; Thomas T. Aoki, M.D.; Susannna L. Cunningham, Ph.D. (Consumer Representative); Susan Dianne Lellock (Patient Representative)

Endocrinologic and Metabolic Drugs Advisory Committee Members Absent:
Michael R. McClung, M.D.; Jorge Plutzky, M.D.; Morris Schambelan, M.D.; Thomas O. Carpenter, M.D.; David S. Schade, M.D.; Margaret E. Wierman, M.D.

FDA Participants:
David Orloff, M.D.; Robert Meyer, M.D.; Julie Golden, M.D.; Jeri El Hage, Ph.D.

Open Public Hearing Speaker:
Peter Lurie, M.D., M.P.H.
Public Citizen's Health Research Group

Issue: New drug application (NDA) 21-865, proposed trade name Pargluva (muraglitazar) Tablets, 2.5 milligrams (mg) and 5 mg, Bristol-Myers Squibb, for the treatment of type II diabetes mellitus.

The agenda proceeded as follows:

Sponsor Presentation
Bristol-Myers Squibb Company:

Introduction	Brian Daniels, M.D. Senior Vice President Global Clinical Development Bristol-Myers Squibb Company
Meeting the Needs for Type 2 DM	David M. Kendall MD University of Minnesota
Muraglitazar Overview	Fred Fiedorek MD Vice President Global Clinical Research Bristol-Myers Squibb Company
Non-Clinical Safety	Mark Dominick DVM, PhD Distinguished Research Fellow Drug Safety Evaluation

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
September 9, 2005
NDA 21-865 Pargluva™ (muraglitazar)
FINAL MINUTES

Clinical Efficacy	Cindy Rubin M.D. Group Director Global Clinical Research Bristol-Myers Squibb Company
Clinical Safety	Rene Belder M.D. Vice President Global Clinical Research Bristol-Myers Squibb Company
Clinical Plans, Pharmacovigilance and Benefit/Risk Conclusions	Fred Fiedorek M.D.
	Committee Discussion
	Break

FDA Review Division Presentation:

Clinical Review	Julie Golden, M.D. Medical Officer Division of Metabolic and Endocrine Drug Products FDA Center for Drug Evaluation and Research
Pharmacology/Toxicology Review	Jeri El Hage, Ph.D. Pharmacologist Division of Metabolic and Endocrine Drug Products FDA Center for Drug Evaluation and Research
	Committee Discussion
	Lunch
	Open Public Hearing
	Break
	Committee Discussion and Questions to the Committee
	Adjournment

Questions to the Committee:

1. Efficacy:

    a. Do the efficacy findings with Pargluva 2.5 and 5 mg daily support use for the proposed indications in the treatment of type 2 diabetes as:
        i. Monotherapy

    YES: 9 NO: 0

        ii. Combination therapy in patients not adequately controlled on metformin or sulfonylurea alone

    YES: 9 NO: 0

    b. Is there adequate evidence that Pargluva 1.5 mg daily is effective for the proposed indications?

Discussion: Before this question was discussed and considered for a vote, a suggestion was made, and granted by the division, to revise the question, omitting the word 'adequate' and

clarifying that the question refers to monotherapy only, as the 1.5 mg dose was only studied for monotherapy. The revised question reads, "Is there evidence that Pargluva 1.5 mg daily is effective monotherapy for the proposed indication? (See transcripts for detailed discussion).

YES: 2 NO: 7

2. Safety:
    a. Do the results of the preclinical studies with muraglitazar and clinical trials with Pargluva 2.5 and 5 mg permit adequate understanding of the risks associated with use, with specific regard to the following issues?

Discussion: The Division provided clarification to this question, instructing the committee to consider the following, as they answer Question 2.a. Parts i.-iv. "At this point, based upon both what has been presented and what has been provided in background material on the preclinical results and the clinical trial results, is there sufficient information at this point, to assess risk versus benefit, in regards to the following issues?"

i. Fluid/electrolyte metabolism

YES: 7 NO: 2

ii. Cardiac effects

YES: 8 NO: 1

iii. Hepatic effects

YES: 9 NO: 0

iv. Muscle effects

YES: 9 NO: 0

(See transcripts for detailed discussion.)

3. Comments/discussion:
    a. Are there patients for whom treatment with Pargluva 2.5 and 5 mg daily poses particular safety concerns?
    b. Are there patients for whom a lower dose (starting and/or maximum) of Pargluva should be considered?
    c. Comment on concerns about adverse effects (e.g., cardiovascular) of Pargluva beyond those expected based on its mechanism(s) of action.
    d. Comment on the discussions regarding the rodent carcinogenicity of Pargluva and questions of potential human risk.
    e. Other issues

Discussion: The Committee discussed this question collectively, providing individual comments as deemed relevant. The committee cited safety concerns in certain patient populations such as those with coronary artery disease with or without congestive heart failure. The committee suggested that safeguards be put in place for those patients. Because no Class I or Class II heart failure patients were studied, concerns were raised about this population utilizing the drug. Additional safety concerns were discussed in the context of the necessity of clinician education, when managing patient therapy with this drug.

Concerns were raised about cardiovascular mortality in the sulfonylurea trial, and the need for outcomes data before using this combination (Pargluva + sulfonylurea).

Carcinogenic data from the presentation was briefly discussed by the Committee and the Division provided clarification about the need for a 7-year monkey study to have complete findings.

Patient representative perspective was provided, in terms of having a drug available that "does what it says it is supposed to do" (lowering the HbA1C), citing that failing to do so creates other health risks throughout the diabetic patient's lifespan.
(See transcripts for detailed discussion).

4. Should Pargluva be approved for the proposed indications?
    a. Monotherapy

YES: 8 NO: 1

    b. Combination therapy in patients not adequately controlled on metformin or sulfonylurea alone
        i. If yes, comment (for each indication) on doses and special populations.
        ii. If no, what additional information is needed (for each indication)?

Discussion: The Committee separated Question 4b. into two parts, answering separately for metformin and sulfonylurea respectively:
-Combination therapy in patients not adequately controlled on **metformin:**
YES: 7 NO: 2

-Combination therapy in patients not adequately controlled on **sulfonylurea:**
YES: 3 NO: 6

Discussion: The Committee cited concerns about cardiovascular adverse events observed in association with use of Pargluva in combination therapy.

The Division asked that the Committee provide additional comments in regards to the effectiveness of Pargluva for the proposed indication, at the lower dose of 1.5 mg, from Question 1b and 3b. The Division requested comments from the Committee about the desirability of the Sponsor developing more data and subsequently marketing the lower dose 1.5 mg Pargluva. Additionally, more choice are better than fewer choices, in terms of dosing and titrating the drug.

The Committee agreed that studies at the 1.5 mg may provide additional information, specifically in regards to beta cell function. The lower dose could potentially be utilized in new onset diabetic patient, but further studies are needed about pancreatic cell preservation. Additionally, the committee would be interested in learning about effects of Pargluva on other biochemical parameters of disease activity and risk in patients with type 2 diabetes.

Some committee members felt that there was not enough evidence to show the drug's effectiveness at the 1.5 mg dose for the proposed indication. Concerns about risks that might counterbalance the benefits of glucose lowering were raised. It was acknowledged that the sponsor's planned long-term outcomes trial will provide valuable information that may shed light on this issue. (See transcripts for detailed discussion).

The meeting adjourned at approximately 2:05 pm.

See transcripts for detailed discussion.