



NEWS RELEASE

# Merck Announces Results of ZOLINZA® (vorinostat) Phase III and IIb Trials for Investigational Use for Multiple Myeloma at American Society of Hematology Annual Meeting

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ZOLINZA in Combination with Bortezomib Achieved Primary Endpoint of Improved Progression-Free Survival in Patients with Relapsed and/or Refractory Multiple Myeloma in Phase III Trial

Merck (NYSE: MRK), known as MSD outside the United States and Canada, announced today that a Phase III study of ZOLINZA® (vorinostat), for investigational use in combination with bortezomib in patients with progressive multiple myeloma, met its primary endpoint, demonstrating a 23 percent reduction in the risk of progression compared to the standard therapy of bortezomib ( $p=0.01$ ). The Phase III results from VANTAGE 088 (Vorinostat in Combination with Bortezomib in Patients with Relapsed/Refractory Multiple Myeloma: A Global, Randomized Phase III Trial) were presented at the 53rd Annual Meeting of the American Society of Hematology (ASH).

Also presented were full results from VANTAGE 095 (Vorinostat in Combination with Bortezomib in Salvage Multiple Myeloma Patients: A Global Phase IIb Trial). Additionally, investigational clinical and pre-clinical vorinostat data across a variety of hematologic cancers were presented in more than 10 oral and poster presentations at the meeting.

"Most patients with multiple myeloma eventually relapse or become resistant to treatment," said Meletios Dimopoulos, M.D., professor and chairman, Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece. "We are encouraged by the results of the investigational use of ZOLINZA in combination therapy in this difficult-to-treat patient population."

Vorinostat (marketed as ZOLINZA®) is a histone deacetylase (HDAC) inhibitor indicated for use in the United States for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following two systemic therapies. ZOLINZA inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2, and HDAC3 (Class I), and HDAC6 (Class II) at nanomolar concentrations (IC<sub>50</sub><86 nM).

VANTAGE 088, a Phase III randomized, double-blinded, placebo-controlled study in patients with progressive multiple myeloma who received between one and three prior treatment regimens, was designed to demonstrate an improvement in progression-free survival (PFS) in patients treated with the combination of the investigational use of ZOLINZA and bortezomib compared to bortezomib alone. The PFS endpoint was assessed by an Independent Adjudication Committee.

Based on the full analysis of 417 PFS events in 637 patients, patients treated with ZOLINZA (n= 317) and bortezomib (n= 320) had a 23 percent reduction in the risk of progression compared to bortezomib alone with a hazard ratio of 0.774 (p=0.01). The observed median PFS was 7.6 months in the ZOLINZA and bortezomib arm, and 6.8 months in the bortezomib arm.

In addition to the improvement in PFS, significant improvement in overall response rate (ORR) was also observed in the combination arm (ZOLINZA and bortezomib, 56 percent; bortezomib and placebo, 41 percent; p<0.0001). The duration of response was 8.5 months in the combination arm and 8.4 months in the control arm. A trend in favor of overall survival (OS) was observed in the ZOLINZA and bortezomib arm, but the difference was not statistically significant (hazard ratio = 0.86; ZOLINZA and bortezomib vs. bortezomib and placebo; p=0.35).

In the Phase III study, significantly more patients treated with the combination of ZOLINZA and bortezomib versus bortezomib alone experienced thrombocytopenia (55 percent vs. 33 percent), diarrhea (62 percent vs. 43 percent), nausea (61 percent vs. 39 percent), vomiting (45 percent vs. 26 percent) and fatigue (40 percent vs. 31 percent) (p<0.05 for all grades). No difference was observed between the discontinuation rates due to an adverse event for vorinostat compared to the placebo arm (21 percent vs. 22 percent).

About Vorinostat in Combination with Bortezomib in Patients with Relapsed/Refractory Multiple Myeloma: A Global Randomized Phase III Trial (VANTAGE 088)

In this investigational study, patients were randomized 1:1 to receive 21-day cycles of bortezomib (1.3 mg/m<sup>2</sup> intravenously; days 1, 4, 8, and 11) in combination with oral ZOLINZA 400 mg/d, or matching placebo, on days 1 to 14. Patients were treated until disease progression, unacceptable toxicities, or withdrawal from the study. The primary endpoint for this trial was PFS (occurrence of 417 PFS events). Secondary and exploratory endpoints

included ORR ( $\geq$  partial response), clinical benefit response (ORR + minimal response), overall survival, time to progression, patient-reported outcomes questionnaires (QLQ-C30, QLQ-MY20), and safety/tolerability.

Six hundred and thirty-seven patients were enrolled from 174 centers in 33 countries across the globe, making this trial one of the largest studies conducted in patients with relapsed/refractory myeloma. The median age of the study population was 62 years (range, 29-86 years). Patients had received a median of two prior regimens (range, 1-3).

#### About Vorinostat in Combination with Bortezomib in Salvage Multiple Myeloma Patients: A Global Phase IIb Trial (VANTAGE 095)

VANTAGE 095 was an open-label, single-arm Phase IIb trial of the investigational use of ZOLINZA plus bortezomib in bortezomib-refractory patients (defined as less than 25 percent response on therapy, or progression during or less than 60 days after completion of therapy) and patients considered to be refractory, intolerant, or ineligible for IMiD-based therapy regimens. Eligible patients were 18 years or older, had measurable secretory multiple myeloma, had received two or more prior anti-myeloma regimens, and relapsed or progressed following prior systemic therapy. Patients received 21-day cycles of bortezomib (1.3 mg/m<sup>2</sup> intravenously; days 1, 4, 8, and 11) plus oral ZOLINZA 400 mg/d on days 1 to 14. If patient had no change as the best response after 4 cycles of treatment or progressive disease after two cycles of treatment, oral dexamethasone 20 mg on the day of and day after each dose of bortezomib could be added to the treatment regimen. Patients were treated until disease progression, unacceptable toxicities, or withdrawal from the study. The primary endpoint was ORR ( $\geq$  partial response) as assessed by an independent adjudication committee. The combination of ZOLINZA and bortezomib demonstrated an ORR of 11 percent according to the European Group for Blood and Marrow Transplant (EBMT) criteria, the primary endpoint.

One hundred and forty-three (143) patients were enrolled from 41 centers in 12 countries across Asia-Pacific, Europe, and North America, with 136 of these patients contributing to the efficacy analysis. The study population was heavily pretreated, having received a median of four prior lines of therapy (range 2-17,  $\geq$  4 prior regimens: 69 percent).

The most common treatment-emergent adverse events regardless of relationship to study drug were thrombocytopenia (70 percent), nausea (57 percent), diarrhea (54 percent) and anemia (52 percent).

Additional details on the design of the studies are available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov), identifiers NCT00773747 (VANTAGE 088) and NCT00773838 (VANTAGE 095).

Selected Important Safety Information for ZOLINZA

ZOLINZA is contraindicated in patients with severe hepatic impairment. ZOLINZA should be used with caution in patients with mild to moderate hepatic impairment.

As pulmonary embolism and deep vein thrombosis have been reported as adverse reactions, physicians should monitor patients for the signs and symptoms of these events, particularly patients with a prior history of thromboembolic events. Treatment with ZOLINZA can cause dose-related thrombocytopenia and anemia. If platelet counts and/or hemoglobin are reduced during treatment with ZOLINZA, the dose should be modified or therapy discontinued.

Gastrointestinal (GI) disturbances, including nausea, vomiting and diarrhea, have been reported and may require the use of antiemetic, antidiarrheal medications and fluid and electrolytes replacement to prevent dehydration. Pre-existing GI disturbances should be adequately controlled before beginning therapy with ZOLINZA. Based on reports of dehydration as a serious drug-related adverse event in clinical trials, patients should be instructed to drink at least 2 L/day of fluids for adequate hydration.

Hyperglycemia has been observed in patients receiving ZOLINZA. Serum glucose should be monitored, especially in diabetic or potentially diabetic patients receiving ZOLINZA. Adjustment of diet therapy for increased glucose, or both may be necessary to prevent hyperglycemia. Electrolytes should be monitored at baseline and periodically during treatment. Hypokalemia or hypomagnesemia should be corrected prior to administration with ZOLINZA.

Severe thrombocytopenia and GI bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Platelet count should be monitored every 2 weeks for the first 2 months.

Patients who are concurrently administered ZOLINZA and coumarin derivatives should be carefully monitored for prolongation of prothrombin time and international normalized ratio.

The most common adverse events observed in clinical trials with ZOLINZA, regardless of causality, were fatigue (52 percent), diarrhea (52 percent), nausea (41 percent), dysgeusia (28 percent), thrombocytopenia (26 percent), anorexia (24 percent), decreased weight (21 percent), and muscle spasms (20 percent).

The most common serious adverse events, regardless of causality, were pulmonary embolism (4.7 percent), squamous cell carcinoma (3.5 percent), and anemia (2.3 percent).

ZOLINZA can cause fetal harm when administered to a pregnant woman. It is not known whether ZOLINZA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug.

Please see U.S. Prescribing Information at: [www.merck.com/product/usa/pi\\_circulars/z/zolinza/zolinza\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/z/zolinza/zolinza_pi.pdf).

## About Merck

Today's Merck is a global healthcare leader working to help the world be well. MSD is a tradename of Merck & Co., Inc., with headquarters in Whitehouse Station, N.J., U.S.A. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit [www.merck.com](http://www.merck.com) and connect with us on Twitter, Facebook and YouTube.

## Forward-Looking Statement

This news release includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. Such statements may include, but are not limited to, statements about the benefits of the merger between Merck and Schering-Plough, including future financial and operating results, the combined company's plans, objectives, expectations and intentions and other statements that are not historical facts. Such statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. Actual results may differ from those set forth in the forward-looking statements.

The following factors, among others, could cause actual results to differ from those set forth in the forward-looking statements: the possibility that the expected synergies from the merger of Merck and Schering-Plough will not be realized, or will not be realized within the expected time period; the impact of pharmaceutical industry regulation and health care legislation; the risk that the businesses will not be integrated successfully; disruption from the merger making it more difficult to maintain business and operational relationships; Merck's ability to accurately predict future market conditions; dependence on the effectiveness of Merck's patents and other protections for innovative products; the risk of new and changing regulation and health policies in the U.S. and internationally and the exposure to litigation and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2010 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site ([www.sec.gov](http://www.sec.gov)).

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ZOLINZA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., USA.

Velcade® is a registered trademark of Millennium Pharmaceutical, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited.

Please see U.S. Prescribing Information for ZOLINZA® at

**[http://www.merck.com/product/usa/pi\\_circulars/z/zolinza/zolinza\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/z/zolinza/zolinza_pi.pdf)** and Patient Information for ZOLINZA® at **[http://www.merck.com/product/usa/pi\\_circulars/z/zolinza/zolinza\\_ppi.pdf](http://www.merck.com/product/usa/pi_circulars/z/zolinza/zolinza_ppi.pdf)**

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