Multiple Sclerosis: AAN 2013

Summary of Poster Information

The posters for the AAN 2013 Meeting were made available yesterday, post market close. In our preview, we had flagged 200+ presentations and posters focused on MS therapies. In this note, we provide some of the takeaways from the key posters.

- **Tecfidera (BIIB, TP$200, OUTPERFORM): (1) ENDORSE Safety (P01.162):** In a note published yesterday (LINK), we flagged that the data presented was not new. This same data had been presented at ECTRIMS 2012. We reiterate our conclusion made and published at the time, that malignancies were not an issue and there was no evidence of increased risks of malignancies. (2) **Pregnancy Data (P02.129):** There was no clinical evidence of Tecfidera increasing risks of fetal abnormalities or adverse pregnancies outcomes (based on limited clinical data). In addition, preclinical data showed that Tecfidera did not impair fertility or teratogenicity in animals at doses causing reductions in maternal weight gain. (3) **Integrated Analysis of DEFINE/CONFIRM (P07.095, P07.097, P07.128):** Incrementally new data illustrated the efficacy of Tecfidera BID/TID based on prior treatment experience. Tecfidera BID/TID generally had favorable effects on ARR across treatment naïve and ABCR-experienced patients, but appeared to be more beneficial in reducing 12-week EDSS progression in treatment naïve (vs. ABCR experienced). We do note that these differences are unlikely to affect how physicians view Tecfidera.

- **RPC1063 (Not covered, PRIVATE):** RPC1063 has the potential to improve on the safety profile than Gilenya. Preclinical studies (P05.157) showed that RPC1063 breaks down into three other metabolites. These four compounds are potent S1P1R agonists with selectivity of >100x over S1P5R and >10,000x over S1P2R, S1P3R, and S1P4R. This higher selectivity could enable RPC1063 to show a better safety profile. The PI trial (P01.178) provided early clinical evidence of RPC1063’s potential improvement in safety. It was shown that dose titration could be used to mitigate the heart rate effects from the first dose. In addition, lymphocyte counts recovered more rapidly after stopping treatment.

- **Alemtuzumab (Sanofi, TP€78, NEUTRAL):** The poster on infection risk (P01.172) showed that a second course of Alemtuzumab did not increase the risk of infection. In addition, previous treatment did not appear to be correlated with infection risk. However, it was notable that lymphocyte counts were not effective in distinguishing high or low infection risks, potentially requiring physicians to be more diligent in monitoring their

Continued on the next page…
patients. The incidence of thyroid and serious thyroid adverse events were 17.3% (vs. 5.7% IFNB-1a) and 0.8% (vs. 0% IFNB-1a) respectively. The incidence of thyroid adverse events peaked in the third year (3-year follow-up); this has been consistent with the PII CAMMS223.

- **Siponimod (Novartis, TPSFr70 OUTPERFORM): BOLD (P01.176):** The AEs for Siponimod observed in BOLD were consistent with previous studies. The initiation of treatment with Siponimod had negative chronotropic and dromotropic effects. The most common AEs are nasopharyngitis, headache, pharyngitis, and lymphopenia.

- **XP23829 (XNPT, TPS10, OUTPERFORM):** The PK/PD data on two formulations were presented. Formulation 1 gave the highest Cmax in the fasted state and a delayed, lower Cmax in the fed state. Formulation 2 gave a lower Cmax, but total exposure was comparable to Formulation 1.

Other observations/conclusions are summarized in Exhibits 1-5.
### Key Presentations — Monday, March 18, 2013

<table>
<thead>
<tr>
<th>Time</th>
<th>Event/Topic</th>
<th>Title</th>
<th>Authors</th>
<th>ID</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Long-Term Efficacy, Safety and Tolerability of Ponesimod in Patients with Relapsing-Remitting Multiple Sclerosis</td>
<td>Mark Freedman, Aaron Boster, Columbus, OH, Oscar Fernandez, Malaga, Spain, Maria Melanison, Carli Pozzi, Miami, Florida, Lance Banker, Miami, Florida</td>
<td>P01.156</td>
<td>We published a note yesterday about this poster. The takeaways are: (1) No new data was presented. (2) The same data had been presented at ECTRIMS 2012. (3) We reiterate our conclusion made and published at the time, that malignancies were not an issue and there was no evidence of increased risks of malignancies.</td>
</tr>
<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Safety and Tolerability of Oral BG-12 (Dimethyl Fumarate) in Relapsing-Remitting Multiple Sclerosis (RRMS): Interim Results from ENDORSE Extension Study</td>
<td>J. Theodora Felix Phillips, Robert Fox, Kristyof Salma, Kartik Raghupathi, Huxing Yuan, Mark Novas, Marianne Sweeney, Vassilia Vigilotta, Katherine Dawson, Ralf Gold</td>
<td>P01.162</td>
<td>- - - - - -</td>
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<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Safety, Tolerability and Patient Evaluation of Peg-Interferon beta-1a Administered Via a Single-Use Autoinjector in Relapsing Multiple Sclerosis: Data from the Phase 3 ATTAIN Study</td>
<td>Peter Casabianca, Shahidul Islam, Alireza Zarrinkafsh, Bjorn Spiering, Serena Hung, Aaron Deykin</td>
<td>P01.163</td>
<td>This detailed analysis showed: (1) Infection risk did not increase with a second dose of Alemtuzumab. (2) Infection risk was comparable between DMARD naïve and experienced. (3) Lymphocyte counts were not effective in distinguishing high or low infection risk.</td>
</tr>
<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Comparison of infection risk with Alemtuzumab and SC-IFNB-1a in Patients with Multiple Sclerosis: Who Experienced Disease Activity While on Prior Therapy (CARE-MS II)</td>
<td>Sybil Wrap, Douglas Arnold, Jeffrey Cohen, Alasdair Coles, Christian Confianteux, Edewd Fox, Hans Hartung, Eva Handreos, Kristyof Salma, Howard Weiner, Tamara Miller, Cary Tewman, Stephen Lake, David Margolis, Michael Panzara, Alastair Compston</td>
<td>P01.172</td>
<td>- - - - - -</td>
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<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Detection, Incidence, and Management of Thyroid Autoimmunity in Comparison of Alemtuzumab and Rebif® in Multiple Sclerosis (CARE-MS I and II)</td>
<td>Tamara Miller, Douglas Arnold, Jeffrey Cohen, Alasdair Coles, Christian Confianteux, Edewd Fox, Hans Hartung, Eva Handreos, Kristyof Salma, Howard Weiner, Stephen Lake, David Margolis, Pedro Oysela, Michael Panzara, Alastair Compston</td>
<td>P01.173</td>
<td>- - - - - -</td>
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<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Phase 2 BOLD Extension Study Safety Results in Siponimod (BAF312) in Patients with Relapsing-Remitting Multiple Sclerosis</td>
<td>Rolf Peter Hartung, Kristyof Salma, Daniel K. E. U., Berndt Mier, Mark Freidman, Olaf Shes, Peter Reckermann, Xavier Montalban, Tjalf Ziemssen, Lixin Zhang-Auberson, Brian Hutter, Erica Rochitte, Erik Wallstrom, Ludwig Happon,</td>
<td>P01.175</td>
<td>- - - - - -</td>
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<tr>
<td>14:00 - 18:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Safety, Tolerability and Pharmacodynamics of a Novel SP1-Modulator in Healthy Adult Volunteers, Results of a Phase 1 Study</td>
<td>Marieke Smits, High Roos, Hegel Smith, Claudia Zim, Jennifer Brooks, Shaola Guiradhi</td>
<td>P01.176</td>
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</tbody>
</table>

**LEGEND**

- **Sessions/Posters**: Peg-IFN
- **Alemtuzumab**: Ocrelizumab
- **Aubagio**: ONO-4641
- **BAF312**: Ponesimod
- **BG-12**: RPC1063
- **Daclizumab**: Tysabri
- **Gilenya**: XP23829
- **Laquinimod**: Other Therapy

**Source:** AAN 2013, Credit Suisse research
### Exhibit 2: Key Presentations – Tuesday, March 19, 2013

<table>
<thead>
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<th>Time</th>
<th>Event/Topic</th>
<th>Title</th>
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</tr>
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<tbody>
<tr>
<td>7:30 - 12:00</td>
<td>Multiple Sclerosis: Pregnancy and Hormonal Influences</td>
<td>BG-12 (Dimethyl Fumarate) and Pregnancy: Preclinical and Clinical Data from the Clinical Development Program</td>
<td>Ralf Gold, J. Theodore Phillips, Eva Hamdova, Amit Bar-Oz, Ludwig Kappos, Huxing Yuan, Mark Novas, Marianne Sweetser, Viassa Viglitta, Robert Fox</td>
<td>P02.129</td>
<td>This study showed: (1) There was no clinical evidence suggesting that Tecfidera increased the risks of fetal abnormalities or adverse pregnancy outcomes based on limited clinical data. (2) There was no preclinical data indicating impaired fertility or teratogenicity in animals at doses causing reductions in maternal weight gain.</td>
</tr>
<tr>
<td>13:00 - 13:15</td>
<td>Multiple Sclerosis: Clinical Trials I</td>
<td>The Safety and Efficacy of Daclizumab HY-P in Relapsing-Remitting Multiple Sclerosis in the SELECTION Extension Study: Primary Results</td>
<td>Gavin Giovannoni, Ralf Gold, Korysztof Salaj, Eva Hamdova, Konar Montaban, Ernst Wilhelm Raduc, Dusan Belocek, Manjil McNeil, Jitesh Rana, Jacob Elkins, Gilmore O'Neill</td>
<td>S01.001</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>13:45 - 14:00</td>
<td>Multiple Sclerosis: Clinical Trials I</td>
<td>Teriflunomide Efficacy and Safety in Patients with Relapsing Multiple Sclerosis: Results from TOWER, a Second, Placebo-Controlled Study</td>
<td>Aaron Miller, Ludwig Kappos, Giancarlo Comi, Christian Contaneous, Mark Freedman, Tomas Olsson, Jerry Wolinsky, Teresa Baguilo, Jean-Luc Delhay, Yan Zheng, Philippe Truffinet, Paul O'Connor</td>
<td>S01.004</td>
<td>This data will be given in an oral presentation.</td>
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### Corporate Therapeutic Update

- **Biogen Idec** (Marriott Hall 1-3)
- **Genzyme, A Sanofi Company** (Hilton Bayfront Ballroom C-H)
- **Novartis** (San Diego Ballroom ABC)

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**LEGEND**

- **Sessions/Posters**
  - Peg-IFN
  - Alemtuzumab
  - Aubagio
  - BAF312
  - BG-12
  - Daclizumab
  - Gilenya
  - Laquinimod
  - Other Therapy

**Source:** AAN 2013, Credit Suisse research
### Exhibit 3: Key Presentations – Wednesday, March 20, 2013

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<th>Time</th>
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<th>Title</th>
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<th>ID</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>14:00 - 14:15</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Longitudinal Stability of Anti-JC Virus Antibody Status in Multiple Sclerosis Patients: Results of STRATIFY-1</td>
<td>Tatiana Plavina, Sophia Lee, Melissa Berman, Amy Natarajan, Sandra Richman, Gary Bloomgren, Barry Ticho, Meena Subramanyam</td>
<td>S30.001</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>14:15 - 14:30</td>
<td>Multiple Sclerosis: Treatment Safety</td>
<td>Natalizumab-Related PML: An Evolving Risk: Identification Paradigms</td>
<td>John Foley</td>
<td>S30.002</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>16:39 - 16:52</td>
<td>Multiple Sclerosis: Novel Treatments</td>
<td>Week 144 Results of a Phase II, Randomized, Multicenter Trial Assessing the Safety and Efficacy of Ocrelizumab in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)</td>
<td>Stephen Hauser, David Li, Peter Calessar, Paul O'Connor, Amit Bar-Or, Frederik Barkhof, Annette Sauter, David Leppe, Donna Masterman, Jeroen Tinbergen, Ludwig Kapoor</td>
<td>S31.004</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis: Treatment Mechanism of Action</td>
<td>Effect of the Sphingosine 1-Phosphate Receptor Agonist ONO-4641 on Circulating Lymphocytes in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Phase 2 DreaMS Trial</td>
<td>Amit Bar-Or, Frauke Zipp, Selmaj Krzysztof, Bryan Due, Timothy Vollmer</td>
<td>P05.153</td>
<td></td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis: Treatment Mechanism of Action</td>
<td>Metabolites of RPC1063 Contribute to In Vivo Efficacy</td>
<td>Fiona L. Scott, Gregg Timony, Jennifer Brooks, Robert Peach, Bryan Clemons, Hans Desale, Mariana Moorjani, Erruthi Bommacharay, Rachel Price, Hong Dadi, Esther Martinborough, Marcus Boehm</td>
<td>P05.157</td>
<td>The analysis showed: (1) RPC1063 is broken down into 3 other metabolites (RP-101988, RP-101075, and RP-101442); (2) RPC1063 and all 3 metabolites are potent S1P1R agonists, with selectivity of &gt;100x over S1P5R and &gt;10,000x over S1P2R, S1P3R, and S1P4R; (3) RP-101898 is the most prevalent metabolite. (4) The concentrations of the metabolites could contribute the pharmacodynamics effects. (5) Preclinical studies suggest that RP-101898 does not distribute in the brain.</td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis: Treatment Mechanism of Action</td>
<td>Favorable Metabolism and Pharmacokinetics of Formulations of XP23829, a Novel Fumaric Acid Ester, in Healthy Subjects</td>
<td>Dmitri Lissin, Wendy Lo, Evra Tai, Katie Zompis, Dan Chan, Son Nguyen, Yinghong Yao, Vima Kim, Jian Zou, Bai Huang, Kenneth Cundy</td>
<td>P05.189</td>
<td>The pharmacokinetics/pharmacodynamics data on two formulations were presented. Formulation 1 gave the highest Cmax in the fasted state and a delayed, lower Cmax in the fed state. Formulation 2 gave a lower Cmax, but total exposure was comparable to Formulation 1.</td>
</tr>
<tr>
<td>17:05 - 17:18</td>
<td>Multiple Sclerosis: Novel Treatments</td>
<td>Clinical Efficacy and Safety of Peginterferon beta-1a in Relapsing Multiple Sclerosis: Data from the Pivotal Phase 3 ADVANCE Study</td>
<td>Peter Catesar, Bernd Kossel, Douglas Arnold, Laura Baxter, Alexey Boyko, Joan Pelletier, Shihang Liu, Ying Zhu, Ali Seldighzadeh, Bjorn Spierling, Serena Hung, Aaron Daykin</td>
<td>S31.006</td>
<td>This data will be given in an oral presentation.</td>
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</table>

**LEGEND**

- **Sessions/Posters:** Peg-IFN, Alemtuzumab, Aubagio, BAF312, BG-12, Daclizumab, Gilenya, Laquinimod
- **Other therapy**

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*Source: AAN 2013, Credit Suisse research*
Exhibit 4: Key Presentations – Thursday, March 21, 2013

<table>
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<th>Time</th>
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<th>Title</th>
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<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00 - 12:15</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Durable Efficacy of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis Patients Who Participated in the CARE-MS Studies: Three Year Follow-Up</td>
<td>S41.001</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>12:45 - 13:00</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Comparison of Early and Delayed Oral Laquinimod in Patients with Relapsing-Remitting Multiple Sclerosis: Effects on Disability Progression at 36 Months in the ALELEGRO Trial</td>
<td>S41.004</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>13:15 - 13:30</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Pre-Defined Subgroups Analysis of TOWER, a Placebo-Controlled Phase 3 Trial of Teriflunomide in Patients with Relapsing Multiple Sclerosis</td>
<td>S41.006</td>
<td>This data will be given in an oral presentation.</td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Effect of BG-12 (Dimethyl Fumarate) in Subgroups of Patients with Relapsing-Remitting Multiple Sclerosis: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies</td>
<td>P07.095</td>
<td>This integrated analysis of DEFINE and CONFIRM showed that Tecfidera BID and TID provided more benefits in ARR, delay in EDSS progression, and clinical MRI outcomes across various patient segments.</td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Clinical Efficacy of BG-12 (Dimethyl Fumarate) in Relapsing-Remitting Multiple Sclerosis: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies</td>
<td>P07.097</td>
<td>This integrated analysis of DEFINE and CONFIRM demonstrated: (1) ARR at 2 years for Tecfidera BID/TID was 49%/49%. (2) Reduction in proportion of patients relapsed at 2 years was 43%/43% for Tecfidera BID/TID. (3) Time to 12-week EDSS progression was 32%/30% for Tecfidera BID/TID. (4) Time to 24-week EDSS progression was 29%/32% for Tecfidera BID/TID.</td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Phase 2 BOLD Extension Study Efficacy Results in Sponsonod (BAF312) in Patients with Relapsing-Remitting Multiple Sclerosis</td>
<td>P07.110</td>
<td></td>
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<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Sponsonod (BAF312) for the Treatment of Secondary Progressive Multiple Sclerosis: Design of the Phase 3 EXPAND Trial</td>
<td>P07.126</td>
<td></td>
</tr>
<tr>
<td>14:00 - 19:00</td>
<td>Multiple Sclerosis:</td>
<td>Clinical Trials II</td>
<td>Clinical Efficacy of BG-12 (Dimethyl Fumarate) for Relapsing-Remitting Multiple Sclerosis (RRMS): According to Prior Therapy: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies</td>
<td>P07.128</td>
<td>Tecfidera BID/TID generally had favorable effects on ARR across naive and ABCR-experienced. Tecfidera BID/TID generally had more beneficial effects on 12-week EDSS progression in naive (vs. ABCR-experienced). Tecfidera BID had a more favorable effect in reducing proportion of patients relapsed on naive (vs. ABCR-experienced). In contrast, Tecfidera TID had a more benefit effect on this same metric in ABCR-experienced (vs. naive).</td>
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**Source:** AAN 2013, Credit Suisse research

**LEGEND**
- Sessions/Posters
- Peg-IFN
- Alemtuzumab
- Aubagio
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- BG-12
- Daclizumab
- Gilenya
- Laquinimod
- Ocrelizumab
- ONO-4641
- Ponesimod
- RPC1063
- Tysabri
- XP23829
- Other Therapy
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- **Market Weight**: The analyst’s expectation for the sector’s fundamentals and/or valuation is neutral over the next 12 months.
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*An analyst’s coverage sector consists of all companies covered by the analyst within the relevant sector. An analyst may cover multiple sectors.

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<th>Rating</th>
<th>Versus universe (%)</th>
<th>Of which banking clients (%)</th>
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<tr>
<td>Outperform/Buy*</td>
<td>43%</td>
<td>(54% banking clients)</td>
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<tr>
<td>Neutral/Hold*</td>
<td>38%</td>
<td>(46% banking clients)</td>
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<tr>
<td>Underperform/Sell*</td>
<td>16%</td>
<td>(40% banking clients)</td>
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<tr>
<td>Restricted</td>
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*For purposes of the NYSE and NASD ratings distribution disclosure requirements, our stock ratings of Outperform, Neutral, and Underperform most closely correspond to Buy, Hold, and Sell, respectively; however, the meanings are not the same, as our stock ratings are determined on a relative basis. (Please refer to definitions above.) An investor's decision to buy or sell a security should be based on investment objectives, current holdings, and other individual factors.
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