Draxxin® (tulathromycin) Injectable Solution: Efficacy in the treatment of experimentally-induced Mycoplasma hyopneumoniae pneumonia in pigs

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Key Points

• Mycoplasma hyopneumoniae remains a key component of Swine Respiratory Disease (SRD) and is an important pathogen for swine producers to control.1

• Two studies were conducted to evaluate the efficacy of a single intramuscular dose of Draxxin® Injectable Solution in the treatment of experimentally-induced M. hyopneumoniae pneumonia in pigs.2,3

• In both studies, the challenge model used a recent U.S. M. hyopneumoniae field isolate.

• Pigs treated with Draxxin had a significantly (*P* < 0.0001) lower percentage of pneumonic lung lesions than pigs in the saline control group (8.52% vs 23.62% in Study A and 11.31% vs 26.42% in Study B).

• Draxxin-treated pigs gained significantly more weight than saline-treated control pigs in both studies (1.48 lb/day versus 1.24 lb/day in Study A, *P* = 0.0207; 1.41 lb/day versus 0.77 lb/day in Study B, *P* < 0.0001).

• Under conditions of the two studies, a single intramuscular dose of Draxxin administered at 2.5 mg/kg was effective for the treatment of experimentally induced pneumonia associated with a recent M. hyopneumoniae field isolate.

**M**ycoplasma hyopneumoniae causes mycoplasmal pneumonia of swine (MPS), one of the most prevalent and costly of swine diseases. A USDA National Animal Health and Monitoring Survey (NAHMS) undertaken in 2001 found that producers in the U.S. thought M. hyopneumoniae was a concern in approximately 20% of nursery pigs on 29% of the farms surveyed. Moreover, in operations with more than 10,000 pigs, mycoplasma-associated disease was considered important in 53% of the sites with nursery pigs and 68% of the sites with finisher pigs. Diagnostically, M. hyopneumoniae was identified in more than 50% of the sites.1 Pigs of all ages are susceptible to MPS; however, disease occurs most often in growing and finishing pigs. Once established, MPS persists in infected herds, varying in severity with season, ventilation, and concentration of swine. Clinical signs include a chronic, nonproductive cough continuing for weeks or months, depressed appetite, listlessness, labored breathing, reduced feed efficiency, nasal discharge, unthrifty appearance, and retarded growth. Stunting may be evident, resulting in considerable variation in size among affected pigs. Even at low levels of infection, MPS causes significant economic losses due to reduced feed efficiency, lower daily...
weight gains, lack of uniformity within groups, decreased carcass price, repeated antibiotic treatment costs, and increased days to reach market weight.\textsuperscript{4}

M. hyopneumoniae also plays a primary role in establishing the mixed infections of the swine respiratory disease (SRD) complex and in potentiating porcine reproductive and respiratory syndrome virus (PRRSV)-induced pneumonia. An Iowa State University study found the majority of severe SRD cases examined were positive for both PRRSV and M. hyopneumoniae.\textsuperscript{5} Pigs infected with PRRSV and M. hyopneumoniae developed pneumonia of greater severity and duration than pigs infected with PRRSV alone. The study concluded that in cases of mixed infection, M. hyopneumoniae potentiated PRRSV-induced disease and lesions but that PRRSV did not influence severity of M. hyopneumoniae infection, suggesting that control of M. hyopneumoniae in mixed infections may be of primary importance.\textsuperscript{5} Other investigators have shown that swine experimentally infected with M. hyopneumoniae are predisposed to pneumonia caused by Pasteurella multocida and Actinobacillus pleuropneumoniae.\textsuperscript{6,7} A survey taken in 2006 by NAHMS underscored the economic damage done by SRD to the pork industry in the U.S. Across sites ranging in size from fewer than 2,000 pigs to more than 5,000, respiratory disease accounted for 44.2\% of nursery deaths and 61.1\% of deaths in grower/finisher pigs.\textsuperscript{8}

Another team of investigators experimentally reproduced postweaning multisystemic wasting syndrome (PMWS) in pigs by dual infection with M. hyopneumoniae and porcine circovirus type 2 (PCV2).\textsuperscript{9} Opriessnig and Thacker associated M. hyopneumoniae infection with increased replication of PCV2, increased severity of PCV2 lesions (specifically lymphoid depletion), and a higher incidence of PMWS. In a subsequent study published in 2008, Rapp-Gabrielson et al found that controlling M. hyopneumoniae was an important tool in reducing respiratory disease and production losses in herds co-infected with PCV2 and M. hyopneumoniae.\textsuperscript{10}

Despite improved management practices, widespread vaccination against MPS, and use of antimicrobial medication, M. hyopneumoniae continues to be a problem worldwide.\textsuperscript{8,11} Whereas numerous investigators have demonstrated the in vitro susceptibility of M. hyopneumoniae to a range of antimicrobials,\textsuperscript{12-17} the pathogen persists under field conditions and in experimental infections.\textsuperscript{1,15,18} As a mucosal pathogen, M. hyopneumoniae colonizes cilia of the trachea, bronchi, and bronchioles,\textsuperscript{1} locations that require antimicrobial agents to reach therapeutic levels in bronchoalveolar fluid if they are to be effective.\textsuperscript{19} Additionally, M. hyopneumoniae lacks a cell wall, making the organism resistant to many therapeutic agents.

**Draxxin (tulathromycin) for Swine**

For all the foregoing health and economic reasons, it is important to evaluate whether newly introduced antimicrobial compounds might be efficacious against M. hyopneumoniae. Draxxin Injectable Solution contains the active ingredient tulathromycin, the first member of a new macrolide class of antimicrobials known as triamilides that have been developed exclusively for use in veterinary medicine.\textsuperscript{20} The product is formulated for intramuscular (IM) injection as a ready-to-use single dose (2.5 mg/kg) that provides a full course of treatment against key bacterial pathogens (Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis, and M. hyopneumoniae) associated with the SRD complex.

The pharmacokinetic (PK) behavior of tulathromycin in swine was demonstrated in how it performs in the respiratory system.
two studies following a single 2.5 mg/kg body weight dose.\textsuperscript{21} In the first study, tulathromycin was rapidly released from the IM injection site, reaching maximum plasma concentration in less than one hour, and was extensively distributed with an approximate 88% bioavailability. In the second study, tulathromycin achieved lung concentrations 61 times the plasma area under the curve (AUC), the parameter that most likely accounts for the overall amount of drug exposure in target tissue (Figure 1).\textsuperscript{22,24} reached a peak lung concentration within 24 hours of dosing; and was slowly released from lung tissue. The high and extended concentrations of tulathromycin in lung tissue are presumed to underpin the high efficacy in vitro that have been observed from a single dose.\textsuperscript{22,24}

In studies of commercial swine herds in Europe and North America, a single dose of Draxxin was demonstrated to have high levels of efficacy against the SRD complex when \textit{M. hyopneumoniae} was present.\textsuperscript{35,36} Moreover, a single dose of Draxxin was shown to have cure rates comparable to multiple doses of cefotiofur sodium, enrofloxacin, florfenicol, or tiamulin.\textsuperscript{24}

The two studies summarized below were conducted to further evaluate the efficacy of Draxxin administered as a single IM dose of 2.5 mg/kg body weight for the treatment of experimentally-induced \textit{M. hyopneumoniae} in pigs. The studies were conducted under close veterinary supervision and were pre-approved by an Institutional Animal Care and Use Committee.

**Study Overview: Design, Assessments, and Analysis**

**Study Design**

The studies were conducted at two geographically separate sites in the Midwestern region of the U.S. (Table 1). Site A acquired 112 clinically healthy female and castrated male crossbred pigs, approximately 6 weeks of age; Site B acquired 101 clinically healthy female and castrated male crossbred pigs, approximately 3 weeks of age. All pigs in both studies were serologically negative for \textit{M. hyopneumoniae}. Prior to initiation of the study, pigs were identified individually with duplicate ear tags and allowed to acclimate for 26 days in Study A and 41 days in Study B. No vaccines for porcine respiratory and reproductive syndrome (PRRS) or \textit{M. hyopneumoniae} were administered during processing. After the acclimation period, pigs at both sites were inoculated once per day for three consecutive days (Days 0 through 2) with 10 mL of a recent field isolate of \textit{M. hyopneumoniae} in a lung homogenate inoculum and returned to their pens. The new isolate was selected in compliance with the US regulatory requirements. On each of the three challenge days, pigs were administered the inoculum intratracheally (8 mL) and intranasally (2mL; 1 mL/naris). In Study A, the inoculum contained approximately $10^5$ \textit{M. hyopneumoniae} organisms per mL; in Study B, from approximately $10^6$ to approximately $10^7$ organisms per mL. The minimum inhibitory concentration (MIC) of tulathromycin for the field isolate was $>64 \mu g/mL$.

In each study, 92 pigs were randomly assigned to one of 12 pens and to treatment groups (Table 2). At each site, 36 pigs

<table>
<thead>
<tr>
<th>Procedures by day of study</th>
<th>Days 0, 1, 2</th>
<th>Day 10</th>
<th>Day 15</th>
<th>Day 20</th>
<th>Day 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pigs inoculated with \textit{M. hyopneumoniae} once per day for 3 consecutive days (8 mL endotracheally; 2mL intranasally)</td>
<td>5 no treatment pigs euthanized</td>
<td>5 no treatment pigs euthanized</td>
<td>5 no treatment pigs euthanized</td>
<td>5 no treatment pigs euthanized</td>
<td></td>
</tr>
<tr>
<td>All saline and Draxxin treatments administered</td>
<td>All treated pigs weighed</td>
<td>All treated pigs weighed</td>
<td>All treated pigs weighed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All saline- and Draxxin- treated pigs euthanized, submitted for necropsy examination</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Table 2 — Treatment groups in studies assessing efficacy of Draxxin for treatment of experimentally-induced \textit{Mycobacteria hyopneumoniae} pneumonia in pigs**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dosage</th>
<th>Regimen</th>
<th>Route</th>
<th>No. pigs</th>
<th>No. treated/pen*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Saline</td>
<td>0.025 mL/kg</td>
<td>Once</td>
<td>IM</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>T2</td>
<td>Draxxin</td>
<td>2.5 mg/kg</td>
<td>Once</td>
<td>IM</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>NTX</td>
<td>No treatment</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Study B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Saline</td>
<td>0.025 mL/kg</td>
<td>Once</td>
<td>IM</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>T2</td>
<td>Draxxin</td>
<td>2.5 mg/kg</td>
<td>Once</td>
<td>IM</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>NTX</td>
<td>No treatment</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>

*There were 6 treated pigs plus 1 or 2 NTX pigs in each pen.

\textsuperscript{a}Volume equivalent to Draxxin Injectable Solution administered at 2.5 mg/kg.

\textsuperscript{b}Dose justification: This dose has been approved by the Center for Veterinary Medicine (CVM) for treatment of swine respiratory disease.
(3/pen) were assigned to the saline (T1) and Draxxin (T2) groups and 20 (1 or 2/pen) to the no treatment (NTX) group. In both studies, at 10, 15, 20, and 25 days after the first day of experimental infection, five pigs from the NTX group were euthanized and submitted for necropsy examination. On Day 10 when 4 of the 5 necropsied NTX pigs showed at least 5% lung involvement, treatment was initiated. All pigs in both studies were weighed at this time, and T1 pigs received an intramuscular dose of saline (0.025 mL/kg body weight) and T2 pigs an intramuscular dose of Draxxin (2.5 mg/kg body weight).

Assessments
Pigs were monitored and scored once daily on Days 13 through 20 for signs of respiratory disease. Attitude signs were scored on a scale ranging from 0 (normal) to 3 (severely depressed); respiration signs, from 0 (normal) to 1 (rapid or abnormal breathing); and coughing signs, from 0 (no cough) to 2 (repeated, marked coughing). On Day 20 all treated pigs on both sites were weighed, euthanized, and submitted for necropsy examination. Pneumonic lung tissue samples and bronchial lavage samples were submitted to the Animal Disease Diagnostic Laboratory, Purdue University (West Lafayette, Indiana) for bacteriology, and M. hyopneumoniae isolation and identification. Lung lesions were inspected visually and physically palpated to determine the amount of consolidation or other lesions in each of the lobes. The percent gross pneumonic lung involvement by lobe was recorded. Each of the seven lobes was scored as a percentage to reflect the proportion of the lung affected. Average daily gain (ADG) per pig was calculated by dividing weight gain by pig days. In both studies, all pigs in the saline control and Draxxin groups were weighed on Day 10 and Day 20. Lung lavage and lung tissue samples were also processed for bacteriology and isolation and identification of other targeted bacterial organisms (Actinobacillus pleuropneumoniae, Pasteurella multocida, Strepococcus suis, and Haemophilus parasuis) at Midwest Veterinary Services, Inc., Oakland, Nebraska, and at the Veterinary Diagnostic Laboratory, Iowa State University.

Table 3 — Disease progression of pigs receiving no treatment (percentage of total lung with lesions)

<table>
<thead>
<tr>
<th>Day of euthanasia</th>
<th>No. pigs</th>
<th>Study A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>10</td>
<td>9.7</td>
<td>2.8</td>
<td>20.6</td>
</tr>
<tr>
<td>15</td>
<td>20.2</td>
<td>7.9</td>
<td>60.0</td>
</tr>
<tr>
<td>20</td>
<td>14.8</td>
<td>4.2</td>
<td>32.2</td>
</tr>
<tr>
<td>25</td>
<td>26.1</td>
<td>10.7</td>
<td>44.5</td>
</tr>
<tr>
<td>10</td>
<td>10.8</td>
<td>6.0</td>
<td>16.3</td>
</tr>
<tr>
<td>15</td>
<td>16.7</td>
<td>7.4</td>
<td>34.0</td>
</tr>
<tr>
<td>20</td>
<td>22.3</td>
<td>13.2</td>
<td>32.5</td>
</tr>
<tr>
<td>25</td>
<td>28.3</td>
<td>18.6</td>
<td>43.8</td>
</tr>
</tbody>
</table>

*Individual lung lobes were weighted using the following ratios: left cranial 10%, left middle 10%, left caudal 25%, right cranial 10%, right middle 10%, right caudal 25%, accessory 10%.
†Number of days after the first day of experimental infection.

Study Analysis
In both studies, the pig was the experimental unit for statistical analysis. The primary efficacy variable was the difference in lung lesion scores between treatment groups. Grossly, the percentage of each lobe involvement was weighted — left cranial, left middle, right cranial, right middle, and accessory lobes each assigned 10% and the left caudal and right caudal lobes each assigned 25% — and summed across lobes to obtain the percentage of total lung with lesions. Reported results are back-transformed least-squares means (LSM).

Summarized secondary assessments included scores for attitude, respiration, coughing, average daily gain, and laboratory results. Lung lesion scores and average daily gain data were analyzed using a mixed linear model. Treatment differences were assessed at the 5% level of significance (P≤ 0.05).

![Figure 2](image-url) — Percentage of total lung with lesions by treatment group and study site

*Significantly (P≤ 0.0001) different from saline-treated pigs.
Results

Deaths/Removals

No deaths in either study were attributed to SRD. One Draxxin-treated pig in Study A was euthanized on Day 18 due to septic arthritis and one saline-treated pig in Study B died on Day 16 due to a gastric ulcer. All data from these two pigs were excluded in the study analyses. Because the accessory lobe from one Draxxin-treated pig in Study A was inadvertently discarded, lung data from this pig were excluded from the analysis.

Lung Lesion Scores

In Study A, NTX pigs euthanized at 10, 15, 20, and 25 days after the first day of infection had lung lesion percentages of 9.7%, 20.2%, 14.8%, and 26.1%, respectively. In Study B, the lung lesion percentages for euthanized NTX pigs were 10.8%, 16.7%, 22.3%, and 28.3% (Table 3). At both sites, the percentage of pneumatic lung lesions was significantly ($P \leq 0.0001$) less for pigs in the Draxxin group than for pigs in the saline group (8.52% versus 23.62% in Study A and 11.31% versus 26.42% in Study B (Figure 2).

Average Daily Gain

ADG was significantly greater for Draxxin-treated pigs than for saline-treated pigs in both studies (Table 4). Draxxin-treated pigs in Study A gained 1.48 lb/day ($P = 0.0207$) and saline-treated pigs 1.24 lb/day, whereas in Study B Draxxin-treated pigs gained 1.41 lb/day ($P \leq 0.0001$) and saline-treated pigs 0.77 lb/day (Figure 3).

Clinical Scores

No significant differences in depression, respiration, or coughing scores between treatment groups were recorded in either study, although fewer Draxxin-treated pigs had positive scores on all three measurements of clinical disease.

Discussion

The clinical results observed in these two studies conducted with a recent $M$. hyopneumoniae field isolate are consistent with previously published assessments of the effectiveness of Draxxin for the treatment of SRD associated with $M$. hyopneumoniae infection. In each of the studies reported here, Draxxin-treated pigs had a significantly ($P \leq 0.0001$) lower percentage of pneumonic lung lesions and significantly ($P = 0.0207$ in Study A; $P \leq 0.0001$ in Study B) higher ADG than saline-treated pigs. Moreover, clinical observations indicated decreased signs associated with SRD in Draxxin-treated pigs compared with saline-treated pigs.

Under conditions of these two studies, a single intramuscular dose of Draxxin administered at 2.5 mg/kg was effective for the treatment of experimentally-induced SRD associated with $M$. hyopneumoniae.

Draxxin Injectable Solution was approved in the U.S. for the treatment of SRD associated with $M$. hyopneumoniae in December 2007. The new label indication further distinguishes the antimicrobial as a significant advance for treating respiratory disease in swine.

Previously licensed for the treatment of $Actinobacillus pleuropneumoniae$, $Pasteurella multocida$, $Bordetella bronchiseptica$, and $Haemophilus parasuis$, Draxxin provides an

Table 4 — Average daily gain in treated pigs

<table>
<thead>
<tr>
<th>Group</th>
<th>No. pigs</th>
<th>Initial mean weight (lb) Day 10</th>
<th>Final mean weight (lb) Day 20</th>
<th>Average daily gain* (lb/day)</th>
<th>Study A</th>
<th>Study B</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Saline</td>
<td>36</td>
<td>64.04</td>
<td>76.46</td>
<td>1.24</td>
<td>0.0723</td>
<td>0.0733</td>
</tr>
<tr>
<td>T2 Draxxin</td>
<td>35</td>
<td>65.23</td>
<td>80.05</td>
<td>1.48</td>
<td>0.0733</td>
<td>0.0951</td>
</tr>
<tr>
<td>T1 Saline</td>
<td>35‡</td>
<td>77.82</td>
<td>85.83</td>
<td>0.77</td>
<td>0.0979</td>
<td>-0.04 to 2.4</td>
</tr>
<tr>
<td>T2 Draxxin</td>
<td>36</td>
<td>77.62</td>
<td>91.70</td>
<td>1.41†</td>
<td>0.0979</td>
<td>-0.04 to 2.4</td>
</tr>
</tbody>
</table>

*Significantly ($P = 0.0207$) different from saline-treated pigs
*Significantly ($P \leq 0.0001$) different from saline-treated pigs

LSM = least squares mean
SE = standard error

*Number of days between initial body weight and final body weight for all pigs in both studies was 10 days.

§Number of pigs in the mean final weight and average daily gain calculations for T1 in Study B = 34.
effective one-dose alternative to repeat-treatment regimens for controlling five key bacterial pathogens associated with the SRD complex. Draxxin is rapidly dispersed from the injection site and plasma, and almost immediately arrives in the lungs where organisms associated with SRD congregate, and then is slowly eliminated. Draxxin extends the period of antimicrobial treatment during times of stress and/or continued pathogen exposure. The complete course of therapy provided by a single dose of Draxxin differentiates the product as the choice treatment for SRD, one that potentially could change the way veterinarians and producers manage their herds. Draxxin should not be used in animals known to be hypersensitive to the product. The pre-slaughter withdrawal time for Draxxin in swine is five days.

Clinical Implications

The studies reported here demonstrate the efficacy of Draxxin in a reproducible SRD challenge model using a recent U.S. M. hyopneumoniae field isolate. This information combined with the results of previous reports demonstrating clinical efficacy in SRD associated with M. hyopneumoniae provides practitioners with evidence for evaluating the suitability of using injectable single-dose Draxxin therapy to treat primary or secondary swine pneumonias due to M. hyopneumoniae.

The following key attributes of Draxxin suggest that the novel antimicrobial meets the needs of producers and veterinarians alike:

- The single-dose treatment regimen provides labor savings and improves dosing compliance compared with orally administered and multi-dose injectable programs.

- One-dose administration also contributes to improved animal welfare and reduced stress as sick pigs need be handled and injected only once.

- The antimicrobial’s unique activity spectrum covers five of the most important bacterial pathogens causing swine respiratory disease.

- The M. hyopneumoniae label indication provides a new option to treat complex SRD associated with five major bacterial pathogens of swine (A. pleuropneumoniae, P. multocida, B. bronchiseptica, H. parasuis, and M. hyopneumoniae).5,8,9
**Antibiotic**

100 mg of tulathromycin/mL

For treatment of infections in beef and non-lactating dairy cattle and intramammary infection in swine only.

**INDICATIONS**

Draxxin (tulathromycin) Injectable Solution is indicated for the treatment of the following infections caused by susceptible organisms:

- **Cattle**: Bovine respiratory disease complex, including pneumonia caused by Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Actinobacillus lignieresii.
- **Swine**: Susceptible intramammary infections.

**DOSAGE AND ADMINISTRATION**

Cattle

Dosage: 2.2 mg/kg (0.5 mL/220 kg) IM. The total volume of injection should not exceed 2 mL/cattle.

Adult: 0.5 mL IM, not to exceed 1 mL/cow. Cattle over 1,500 lbs may receive a second dose 10 days later. The total dose should not exceed 4 mL/cow.

**ADVERSE REACTIONS**

Cattle

In a field study, four treated cattle with Draxxin at a 2.2 mg/kg injectable contain tartrazine, a colorant in the formulation. One treated cattle exhibited no adverse reactions, one cattle exhibited severe lameness, one cattle exhibited diarrhea, and one cattle exhibited anorexia.

**PRECAUTIONS**

Cattle

Draxxin should be used with caution in animals with pre-existing kidney disease. The following precautions are recommended for the treatment of infections in cattle:

- **Pregnancy**: Do not use in pregnant cattle.
- **Lactation**: Do not use in lactating cattle.

**SUSPENSION**

The effectiveness of Draxxin in preventing or controlling infections in cattle and swine has not been evaluated in clinical trials.

**EFFECTIVENESS**

- **Field trials**
- **Laboratory tests**

**REFERENCES**

The use of Draxxin (tulathromycin) Injectable Solution is contraindicated in animals previously sensitized to tulathromycin or related macrolides.

**ANIMAL SAFETY**

**STORAGE CONDITIONS**

Draxxin (tulathromycin) Injectable Solution is available in the following parenteral formulations:

- **Solutions**
- **Powders**

**HOW SUPPLIED**

*This is a sample page from a larger document. The full document contains more detailed information.*
References

2. Data on file, Pfizer Inc, Study 1121C-60-03-209.