Three (3), alternative, long acting MPH formulations are currently available and approved for once daily dosing in the treatment of pediatric ADHD: 1) Ritalin LA, 2) Concerta, 3) Metadate CD and 4) Methylin ER. All these formulations combine extended and immediate release (ER, IR) components resulting in different release patterns. Ritalin LA produces greater exposure to MPH and higher MPH concentrations during the first 6 hours post dosing, a time of great importance in the school day [the first peak concentration (Cmax), and time to the first peak (Tmax1) is reached in 1-3 hours]. Concerta peaks after 1-2 hours then increases gradually over the next several hours with a Cmax of 6.8 hours. Metadate has an early peak concentration about 1.5 hours after dose intake, and a second peak concentrations (median) about 4.5 hours after dose intake. Methylin ER has duration of action of approximately 8 hours.

MTS is supposed to have an advantage to current formulations by providing a once daily administration, hence, minimizing problems associated with taking oral MPH immediate release during the school day. There is no other current transdermal formulations.

C. Important Milestones in Product Development

Noven submitted an IND for Methylphenidate Transdermal System (MTS) on 12/12/97. The End-of-Phase II meeting was held on 02/04/00, after completion of two Phase II trials in pediatric patients (Studies N17-002 and N17-003). The following, incomplete list of items were agreed upon at that meeting:

- It was agreed that the 3 month toxicology studies may be waived due to the partial similarity of metabolic exposure between the oral and transdermal routes of administration in humans, as well as to the fact that it appears that rats may not metabolize methyphenidate stereoselectively after oral dosing, and thus previously performed oral rat studies may mimic human transdermal dosing in this regard. However, in order to conform with current regulatory standards, standard reproduction studies will be required to support inclusion of substantial numbers of females of childbearing potential in clinical trials (Segment II) and for approval of an NDA (Segment III).
- The sponsor was advised that although the application appears to qualify under 505(b)(2), the issue of differences in exposure to the *d* and *l* forms from the different route of administration need to be addressed in the NDA in relation to the approved oral racemate product.
- It was agreed that the dermal sensitization study might be conducted in adults; however, consultation from the FDA Division of Dermatological Drug Products will be sought. Noven is planning to monitor for dermal adverse events during the pivotal pediatric clinical study.
- Since there is also an additional concern with assessing local dermal carcinogenic potential in addition to the systemic carcinogenic potential

with this dosage form, a three-month dermal study should be performed in animals.

- The abuse potential of the methyphenidate patch was discussed. Noven believes that this dosage form is less likely to be abused warranting a more lenient schedule. Several ways to support this position were discussed. It was agreed that Dr. Klein's group would be further consulted on this issue.
- Although, dosing of the drug on a weight basis was discussed, it was agreed that the dosing approach proposed by Noven would be acceptable. The sponsor was also advised that per Division policy, the description of a pivotal clinical trial in the product labeling is usually restricted to the primary efficacy measure only; however, if two endpoints are chosen, they must both be statistically significant.

A pre-NDA meeting was held on 04/19/01 based upon Noven's expectations of a positive response for the pivotal Phase III trial N17-010. The discussion focused on the March 15, 2001, briefing package, including specific questions pertaining to CMC issues and the ISS. At that meeting the following was agreed upon:

- FDA inquired whether Noven had investigated the extractability of the patch in an alcoholic solution. Noven responded that they had looked at many solvents and found that it took 4-6 hours to extract anything during which time the drug is also undergoing degradation. They also added that methylphenidate immediately degrades in [redacted]. However, Noven agreed to further investigate the solubility of the patch in alcoholic solutions from 10% to 100% ethanol.

- FDA asked for the sponsor to compare plasma levels of the *d* and *l* enantiomers achieved in the animal studies with those in humans and said this can be important for complementing the human safety database, since humans are exposed to greater levels of the *l* enantiomer with the patch than with oral dosing. Noven responded that they feel that the animal studies provide adequate coverage.

- FDA said the proposals as presented in the briefing booklet were acceptable, but requested additional PK information on gender effects and a comparison of *d* and *l* levels between children and adults from 0-16 hours for the to-be-marketed patch.

- For the ISS, FDA would like to see threshold values set for laboratory and vital signs for outlier criteria. Noven agreed to provide FDA with specific values for comment.

- FDA advised that the issues raised in the comments (previously provided by fax to Noven) from the FDA Dermatology Division for the skin irritation and contact sensitivity protocol should be addressed. Noven responded that they have monitored for dermal adverse events in the clinical studies and no serious adverse events have been reported. They also pointed out that the site of application of the patch would be rotated on a daily basis in the clinical setting.

- FDA then questioned whether there could be any PK changes from application to irritated skin. Noven responded that increased absorption (bolus release) was unlikely at steady-state conditions since the absorption is mainly driven by the contents of the patch, which is a matrix design. Noven also cited evidence from in vitro cadaver skin stripping studies, which showed only a small increase in initial absorption prior to steady state. They also added that the product labeling would discourage usage on irritated skin, similar to the labeling for other transdermal products.

- Noven then presented the preliminary findings for the efficacy study, N17-010. A recent analysis showed that the patch could not be differentiated from the placebo for the primary efficacy variable. Noven offered various explanations for this and sought FDA's input for designing a repeat small study. One option being considered by Noven is to [redacted] Noven will [redacted] FDA suggested considering the input profile of the formulation and perhaps looking at efficacy over the course of the day.

- The CDER CSS advised that Noven must make a convincing case to support down scheduling of the patch formulation since the drug substance is currently listed in schedule II. They asked that the issues raised in a recent letter in response to an October 31, 2000, meeting between Noven and the CSS should be addressed. In particular, they suggested that Noven investigate whether abuse could occur through sharing of the patch between subjects. Noven felt that this was unlikely due to the matrix design of the patch.

E. Important Issues with Pharmacologically Related Agents

Immediate and sustained oral formulations have been associated with insomnia, anorexia, weight loss, decreased growth, abdominal pain and hypertension.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

1. The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1) raises concerns in there review whether the MTS formulation is clinically appropriate for MPH based upon the following identified issues. The reader is referred to this review for a detailed discussion of these and other pharmacokinetic issues related to this formulation.

- The PK studies show an initial lag in drug absorption (mean 3 hours, range 1-5 hours). A slow steady increase in concentration follows with C_{max} being occurring around 10-12

hours. Removal of the patch at 16-hour is followed by an elimination half-life of 3 hours. Higher doses result in the plateau being reached earlier as the rate of elimination becomes equal to the rate of delivery earlier. Potential clinical implications related to this are: 1) the lack of clinical efficacy in the morning, 2) the occurrence of adverse events in the afternoon and overnight (e.g. appetite suppression, insomnia), 3) the predisposition to depression with drug withdrawal, and 4) a actual usage of larger patches and shorter duration resulting in a high residual content.

- MTS exposure doses are 3.5 fold higher for *d*- methylphenidate (*d*-MPH) and 173 fold higher for *l*-methylphenidate (*l*-MPH) as compared to oral administration with Ritalin. In addition, the expected mean *l*-MPH Cmax is higher than the mean Cmax of *d*-MPH of around 15 ng/ml normally achieved with oral dosing. In addition, the AUC for *l*-MPH (which is around 50% of the AUC for d-MPH with transdermal adminis-tration) is also likely to be relatively high relative to the usual *d*-MPH AUC achieved with oral dosing. Thus these higher exposures to *l*-MPH relative to oral administration raises the question of whether there is adequate historical safety information in patients or subjects to adequately assess the safety of *l*-MPH exposure.

- Skin inflammation is associated with a 3-fold increase in Cmax and AUC. Heat increases the delivery rate and extent of delivery by 2-2.5 fold.

- Dermal tolerability studies showed mild erythema in 50 % of subjects by day 5. Dermal sensitization is possible.

- Adhesion was found to be excellent for short duration of wear, but the effects of bathing, swimming, and exercise were not studied.

2. The Division of Dermatological and Dental Drug Products (HFD-540) reviewed concluded that the MTS patch was irritating (MPH > adhesive), and suggested that this be reflected in labeling. MTS may have the potential to act as a sensitizer as evidenced by 3 % (3 out of 99) of the subjects in study N17-008 showing reactions suggestive of sensitization in the challenge phase of the study. Furthermore, due to irritancy, many subjects may not have been able to be adequately induced because of abbreviated induction periods. The reviewer notes that photo-irritation and photosensitization studies do not appear to

have been conducted by the Sponsor and that they were no discussion found regarding these studies. The review states that "generally, such studies can be waived if no components of the study product absorb in the ultraviolet spectrum. With transdermal patches, a Sponsor might support a request for waiver of photosafety studies, by adequately establishing that their product does not transmit ultraviolet light; however, it is noted that the Sponsor describes their product as "[redacted]" (Volume 3, p. 7). It is acknowledged that the intended site of application (buttocks) is not generally considered a sun- exposed area. However, scenarios could be envisaged that might result in exposure to sun- exposed skin. Given the irritancy of the product, it is possible that some subjects might remove the MTS unit over the course of the day. Alternatively, the patch could fall off. Both scenarios might allow for the potential mishandling of the patch e. g., exposure of product to a body site for which it is unintended (by mis-application), or to other children for whom it is unintended." The reader is referred to this review for a complete discussion of these issues.

3. The Division of Biometrics I (HFD-710) confirmed the results reported by the Sponsor in the LOCF analysis for the primary efficacy, Teacher Rated Inattentive/Overactivity Scale in the first and subsequent phase III studies, N17-010 and N17-018. The reader is referred to this review for a complete discussion of statistical issues related to design, results and adverse events. Study N17-010 was not efficacious on this endpoint, while study N17-018 which used a wider dose range and an additional week of treatment was efficacious on this endpoint ($p < 0.0001$). However, an increased rate of adverse events occurred in study N17-018: 50% experienced anorexia in the MTS group compared to 2% for the placebo group, and 29% experienced insomnia in the MTS group compared to 5% for the placebo group. Study N17-018 also showed a significant interaction ($p=0.0063$) between baseline Teacher I/O score and treatment suggesting that treatment was more effective for those most severely affected at baseline (significant in favor of MTS for baseline Teacher I/O scores ≥ 5). However, a non-parametric (Wilcoxon test) analysis showed that "the treatment effect was robust and was not a cause for concern." Study N17-010 which showed no treatment difference on the primary endpoint showed a significant treatment by center interaction ($p=0.01$) thoughtout [with the average reduction in the Teacher I/O being larger for the placebo group in 8 of the 20 centers (and smaller in 12)].

4. The Good Clinical Practice Branch I & II (HFD-46/47), Division of Scientific Investigations, inspected 3 sample sites that enrolled a high number of subjects in Study N17-018. The sites were Dr. Helfing Salem of OR, Dr. Lopez of Maitland FL and Dr. Wynn of Wynn Milwaukee WI. The data from the 3 sites was found to be acceptable in support of the NDA. Dr. Lopez's site had a delay in obtaining IRB approval prior to an increase in subject enrollment.

5. The Controlled Substance Staff, HFD-009 evaluated the Sponsor's suggestion that MTS had a lower potential of abuse and diversion than the oral MPH product as a result of its sustained-release formulation. Controlled Substance's full review is pending at the time of this report[20]. The degree to which MPH and its demethylated breakdown product, ritalinic acid could be extracted from MTS with common household liquids and organic solvents (e.g., a non-professional person) was assessed by the Controlled Substance Group. This was done because it has been documented in the literature that abuse of MPH by injection has followed the extraction of Ritalin tablets. They showed that "that significant amounts of MPH and ritalinic acid could be extracted from 25 cm^2 MTS in water, isopropanol, acetone, isooctane, and lighter fluid. They concluded that MPH could be extracted from the patch matrix with various alcoholic beverages and that MTS could be diverted for the purpose of extracting the active ingredient for ingestion or other abuse. Minimal technical expertise and minimal laboratory equipment were needed to isolate and purify methylphenidate for abuse from the patches".

   In auditing Study N17-021, the Controlled Substance Division identified a substantial number of missing MTS patches for Patient # 18/16.

6. The Division of Medication Errors and Technical Support, HFD-420 reviewed the proprietary name, [redacted] to identify any additional proprietary or established names that have the potential for confusion with [redacted]. They had no objections to the use of this proprietary name. Draft labels and labeling were provided for review. However, they do not include artwork and font sizes that will be used in the final printed labels and labeling. Therefore, it was not possible to fully assess the safety of the labels and labeling based upon these drafts.

[20] A subset of the full review relating to the extraction process was provided by Controlled Substances.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Nine (9) PK and PD studies were conducted and are identified in Table 5 in the Appendix. The reader is referred to the review of MTS by OCPB/DPE-1.

IV. Description of Clinical Data and Sources

A. Overall Data

The clinical data for this NDA comes from 18 studies, which are identified in the Appendix. Nine (9) of these were pharmaco-kinetics (PK) and pharmaco-dynamics (PD) studies[21] with one (1) of these, also being a phase II study preliminarily looking at efficacy (N17-002). Three of these studies were phase II, single center, crossover dose-finding studies[22] in children subjects with ADHD. One was a single center open labeled, skin irritation and sensitization study (N17-008). Five (5) of these studies were phase 3 trials, of which, three (3) were open-label, long term or continuation studies[23] and two (2) were multicenter, randomized, double-blind, placebo-controlled dose titration studies [Studies N17-010 (010) and N17-018 (018)] in children with ADHD who attended a community class-room setting.

B. Tables Listing the Clinical Trials

The following tables summarizing the clinical trials are present in the Appendix: Table 4 shows the two placebo controlled efficacy trials, N17-019 and N17-018; Table 6 shows the uncontrolled, long-term, safety and efficacy studies; Table 7 shows the Phase II trials; and Table 5 shows the pharmacokinetic studies.

C. Postmarketing Experience

The NDA application does not include any post-marketing data.

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[21] Pediatric ADHD PK and PD Studies: N17-016, N17-005 and N17-002; Healthy Adult PK and PD Studies: N17-004, N17-006, N17-017 and N17-014; and Adult Stimulant Users: N17-007 and N17-012.

[22] Phase II Studies: N17-003, N17-009 and N17-015.

[23] Phase III Open Label Studies: N17-011, N17-013 and N17-021

D. Literature Review

The sponsor performed a literature search and provided eighty-nine (89)-published papers on various topics related to ADHD and, or, methylphenidate (MPH) or stimulant use. ADHD articles included information on: diagnosis in children and adolescents, neuro-psychological and behavioral correlates, epidemiology, treatment strategies, mediators of treatment response, behavioral versus pharmacological interventions, medication effects in structured classroom environments, and the dose effects of and the effects of stimulants on classroom academic and social behavior. Articles related to the use of MPH or other stimulants in ADHD including a review of stimulant use(s); a PDR package insert for MPH; the psychological and behavioral effects of MPH or stimulant use; the effects of MPH in classroom and, or, naturalistic settings; various comparisons of short acting and long acting MPH formulations; comparisons of MPH with ADDERRALL or dextroamphetamine; and comparisons of sustained release and standard MPH effects on cognitive and social behavior. Three (3) articles dealt with the abuse potential of MPH. Articles related to ADHD instruments of diagnosis included the NIMH diagnostic interview schedule for children version 4 (DISC-4), an assessment manual for CGI and normative data on the Revised Connors parent and Teacher rating Scales. Other articles related to the development and testing of transdermal products as it related to toxicity, contact allergy, comparison of rabbit and human skin responses to certain irritants, etc. Additional articles included in-vitro inhibition of p450 by MPH, enantio-selective PK and PD of MPH in ADHD, etc.

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review was divided into two general sections-efficacy and safety review. The review of efficacy focused on the individual pivotal studies. There was no examination of pooled efficacy data. Safety data was examined starting from the integrated summary of safety (ISS). Serious adverse events and adverse dropouts were reviewed for both pivotal studies for the proposed ADHD claim. Data from controlled clinical trials of ADHD were pooled, when appropriate, to explore common and drug related adverse events, treatment related changes in laboratory analytes, changes in vital signs, and other specific searches.

B. Overview of Materials Consulted in Review

The electronic version of this submission was used for the entire clinical process. The NDA application was generally

complete. For the most part, the clinical review drew only from materials included in the NDA submission.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The submission was checked for internal consistency. Various narrative summaries were checked against the table listings to help ensure the accuracy of some of the safety data. The Division of Scientific Investigations (DSI) was consulted and they made sample site visits.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials were conducted in accordance with Good Clinical Practice Guidelines (GCP).

E. Evaluation of Financial Disclosure

The sponsor provided the required financial disclosure information under 21 CFR Part 54.2 for the Principal Investigators and Subinvestigators in Studies N17-010, N17-011 and N17-018. None of the 41 Investigators or any of the Subinvestigators identified in these 3 studies had disclosable financial information.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The first, multiple dose titration [6.25 cm^2 (13.8 mg), 12.5 cm^2 (27.5 mg) and 25.0 cm^2 (55.0 mg], placebo-controlled phase III study (N17-010) showed that MTS was not more effective than TS in reducing ADHD behaviors as measured by the Teacher I/O (Inattentive/Overactivity) Factor subscale IOWA during a 3-week evaluation period. The second, multiple dose, placebo-controlled phase III study (N17-018) showed clinical efficacy on this same endpoint by titration to a wider dose range (up to 50 cm^2) and an additional week of MTS exposure.

B. General Approach to Review of the Efficacy of the Drug

The review of clinical efficacy of MTS for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children between the ages of 6-12 years focused on the two (2) parallel group, randomized, double blind, placebo controlled, flexible dose titration studies (010, 018) on an individual basis.

C. Detailed Review of Trials by Indication

Study 010: This study was conducted over the 5-month period from 9/12/2000-2/16/2001 by the investigators and at the sites identified in Table 3 the Appendix.

Objective(s): The primary objective was to assess the safety and efficacy of MTS compared with placebo in children, ages 6-12 years, diagnosed with ADHD. The secondary objective was to assess skin tolerance and patch adhesivity (i.e., adhesion) of the MTS.

Population: The subjects were to be healthy outpatient children (6-12 years) with an IQ ≥ 70 with a primary DSM-IV diagnosis of ADHD[24] and who were enrolled in ≥ Grade 1 and who demonstrated a need for ADHD medication. Subjects were either currently treated or treatment-naive with a standard ADHD medication. Subjects had to be in a school setting where a single teacher interacted with the child for a full school day so that valid assessments of behavior could be made on specified days.

Design: Following baseline, subjects were randomized to either placebo TS or MTS [6.25 cm^2 (13.8 mg)]. At week 1 or 2, the study medication could be titrated (up, down, or, same: [6.25 cm^2 (13.8 mg)][12.5 cm^2 (27.5 mg); or, 25.0 cm^2 (55.0 mg)]) based upon efficacy ratings (e.g. Subscale and Factor Scores from the Pittsburgh Modified Connors Rating Scale and the CGI-I) and evaluations of safety and patch tolerability. The final evaluation occurred at week 3 of the double-blind period. Concomitant use of psychopharmacological drugs (e.g. amphetamine, other stimulants, tricyclic anti-depressants, selective serotonin reuptake inhibitors, neuroleptics, anxiolytics, etc) was prohibited.

Of the 213 subjects who entered the double blind period, 210 were analyzed for efficacy (intent to treat). The treatment groups were comparable in demographic and baseline characteristics (mean age of enrollment, mean age the onset of ADHD, sex [males > female 3:1], had combined inattentive and hyperactive/impulsive ADHD, degree of severity [60% moderately ill on CGI-S], and baseline mean scores for the teacher I/O Factor). A

[24] Psychiatric history; Parent version of the NIMH Diagnostic Interview Schedule-Children (C-DISC-4.0); Disruptive Behavior Disorders (DBD) Parent/Teacher Rating Scale done by a teacher who interacted with the child in a classroom setting for at least 2 weeks prior to completion of the DBD.

table showing baseline demographic characteristics is included in the Appendix.

Assessments: Screening assessments were to include a medical and psychiatric history [C-DISC-4.0] and evaluation, vital signs, measurement of height, recording concomitant medications and clinical laboratories. The primary efficacy measure was the Teacher's IOWA-Conners Inattention/ Overactivity (Teacher I/O) Rating Scale. The secondary efficacy measures were the Parent I/O Factor subscale IOWA-Connors Rating Scale, the Teacher + Parent O/D (Oppositional/Defiance) Factor of the IOWA-Conners Rating Scale, Pittsburgh Modified Conners Rating Scale Derived Scales (Abbreviated Conners, Teacher + Parent Peer Relations and Teacher Effective Normalization Factor) and the Clinical Global Impressions-Improvement (CGI-I) Rating Scale.

Safety monitoring assessment included physical examinations, vital signs (sitting BP, heart rate and temperature), weight, clinical laboratories and recording of adverse events.

The Teacher and Parent I/O were completed once weekly before each visit (baseline, week 1, 2 and 3). CGI- S scores were completed at baseline and CGI-I was assessed weekly (week 1, 2 and 3). The DBD Parent/Teacher Rating Scale and the Pittsburgh Modified Conners Rating Scale were provided to the teacher and parent at screening and returned to the Investigator at Baseline.

Analysis Plan: The primary outcome was the change from baseline on the teacher I/O Factor of the IOWA-Conners Rating Scale. These data were analyzed using an analysis of covariance (ANCOVA) model that includes treatment group (TG) and center (C) main effects and the TG by C interaction effect. The baseline score served as the covariate. The significance of the within-group mean changes from baseline was assessed using paired t-tests, and 95% confidence intervals were determined for the mean change from baseline.

Study Subjects: Two hundred and ten (210) subjects were randomized to MTS (N=101) or TS (N=109) receiving at least a single dose (ITT, ITT-Safety). Ninety-two (92) subjects in the MTS group and 97 subjects in the TS group completed all visits. Twenty-five (25) subjects (MTS, N=10; TS, N=14) were excluded from the final efficacy evaluation (Per Protocol Efficacy Population [PPE]) secondary to protocol violations, as indicated in the Table in the Appendix. The rates of discontinuation due

to adverse events, protocol violation, and other reasons were similar in the two groups. Discontinuation because of lack of efficacy was more common in the TS group (5.5% of patients) than in the MTS group (1.0%). There were no significant differences between either ITT group with respect to duration of exposure (MTS: 20.5 days, TS: 20.8 days) or mean wear time for the patches, as indicated in the Appendix. The percentage of subjects wearing the different patch sizes at the final visit were 6.25 cm 2 (MTS: 8.9, TS: 10.1), 12.5 cm^2 (MTS: 24.8, TS: 11.9) and 25 cm^2 (MTS: 66.3, TS: 78), and are indicated in a Table in the Appendix. Of the subjects in the MTS group, 62.4% reported at least one AE over a total drug exposure time of 45.1 patient-months compared to 50.5% in the TS group over a total drug exposure time of 45.1 patient-months. The Investigators considered none of the AE's serious (Table-Appendix). Three (3) subjects in the MTS group and 2 in the TS group were withdrawn from the study because of adverse events. The AE's in the MTS group consisted of insomnia (N=2) and depersonalization, hallucinations and manic reaction (N=1), while the AE's in the TS group consisted of headache (N=1) and leg cramps (N=1). A Table of AE's leading to premature discontinuation is provided by the Sponsor and included in the Appendix.

Results: There was no statistical difference between MTS and TS on (placebo) groups on the primary efficacy, the Teacher I/O Rating Scale. The LOCF analysis indicated a change from baseline of -2.3 and -1.5 scale units for the MTS and TS groups, respectively (p= 0.7927). Study 010 showed a significant change from baseline between the treatment groups in the Parent Rated I/O Factor (p< 0.0001) and the CGI.

Conclusion(s): This study showed no difference between the MTS and TS (placebo) groups on the primary efficacy, the Teacher I/O Rating Scale.

Study 018: This study was conducted over a 4.5-month period from 10/23/2001-03/05/2002 by the investigators and at the sites identified

Objective(s): The primary objective was to assess the safety and efficacy of MTS compared with placebo in children, ages 6-12 years, diagnosed with ADHD. The secondary objective was to assess skin tolerance and patch adhesivity (i.e., adhesion) of the MTS.

Population: The subjects were to be healthy outpatient children (6-12 years) with an IQ ≥ 70 with a primary DSM-IV diagnosis of ADHD[25] and who were enrolled in ≥ Grade 1 and who demonstrated a need for ADHD medication. Subjects were either currently treated (taking MPH ≤ 60 mg/d or other psychostimulant monotherapy) or treatment-naive with a standard ADHD medication. Subjects had to be in a school setting where a single teacher interacted with the child for a sufficient part of the school day so that valid assessments of behavior could be made on specified days.

Design: Following baseline, subjects were randomized to either placebo TS or two starting MTS doses [12.5 cm^2 or 18.75 cm^2]based on weight, or, the previous oral dose. At week 1, 2, or 3, the study medication could be titrated (up, or, kept the same: [6.25 cm^2 – 50 cm^2]) based upon efficacy ratings [room for improvement on the Teacher I/O (≥5) or CGI-S (≥3)] and evaluations of safety and patch tolerability. Downward titration could occur only after the subject reduced wear time from 12 to 9 hours. The final evaluation occurred at week 4 of the double-blind period. Concomitant use of psychopharmacological drugs (e.g. amphetamine, other stimulants, tricyclic anti-depressants, selective serotonin reuptake inhibitors, neuroleptics, anxiolytics, etc) was prohibited.

Of the 211 subjects who entered the double blind period, 207 were analyzed for efficacy (intent to treat) and 211 for safety with 140 (66.4 %) ending up completing the study. The treatment groups were comparable in demographic and baseline characteristics (mean age at enrollment, mean age at onset of ADHD, sex [males > female 3:1], had combined inattentive and hyperactive/impulsive ADHD, and degree of severity [52% moderately ill on CGI-S]. A table showing baseline demographic characteristics is included in the Appendix.

Assessments: Screening assessments were to include a medical and psychiatric history [C-DISC-4.0[26]] and evaluation, vital signs, measurement of height, recording concomitant medications and clinical laboratories. The primary efficacy measure was the Teacher's IOWA-Conners Inattention/ Overactivity (Teacher I/O) Rating Scale. The secondary efficacy measures were the Parent

[25] Psychiatric history; Parent version of the NIMH Diagnostic Interview Schedule-Children (C-DISC-4.0), which was not needed if subject was on a stable dose of MPH for ≥ 4 weeks and the diagnosis was made within 12 months of study start; Disruptive Behavior Disorders (DBD) Parent/Teacher Rating Scale done by a teacher who interacted with the child in a classroom setting for at least 2 weeks prior to completion of the DBD with the child being of medications for 5-7 days prior to DBD administration.
[26] C-DISC-4.0 was not done if the subject was taking MPH, and the diagnosis was made within 12 months of study entry.

I/O Factor IOWA-Connors Rating Scale, the Teacher + Parent O/D (Oppositional/Defiance) Factor of the IOWA-Conners Rating Scale, Pittsburgh Modified Conners Rating Scale Derived Scales (Abbreviated Conners, Teacher + Parent Peer Relations and Teacher Effective Normalization Factor) and the Clinical Global Impressions-Improvement (CGI-I) Rating Scale.

Safety monitoring assessment included physical examinations, vital signs (sitting BP, heart rate and temperature), weight, clinical laboratories and recording of adverse events.

The Teacher and Parent I/O were completed once weekly before each visit (baseline, week 1, 2, 3 and 4). CGI- S scores were completed at baseline and CGI-I was assessed weekly (week 1, 2, 3 and 4). The DBD Parent/Teacher Rating Scale and the Pittsburgh Modified Conners Rating Scale were provided to the teacher and parent at screening and returned to the Investigator at Baseline. The teacher had to endorse at least 2 symptoms on the DBD.

Analysis Plan: The primary outcome was the change from baseline on the teacher I/O Factor of the IOWA-Conners Rating Scale to the last follow-up appointment (LOCF). These data were analyzed using an analysis of covariance (ANCOVA) model that included treatment group (TG) and center (C) main effects and the TG by C interaction effect. The baseline score served as the covariate. The significance of the within-group mean changes from baseline was assessed using paired t-tests, and 95% confidence intervals were determined for the mean change from baseline. The primary variable, Teacher I/O score was also evaluated at weekly intervals during the double-blind portion of the study using the observed data rather than LOCF.

Study Subjects: Two hundred and ten (211) subjects were randomized to MTS (N=106) or TS (N=105) receiving at least a single dose (ITT, ITT-Safety). Ninety-one (91) subjects in the MTS group and 49 subjects in the TS group completed all visits. A table listing the disposition of all subjects is included in the Appendix. Of the 211 subjects who entered the double blind period, 207 were analyzed for efficacy (intent to treat) and 211 for safety with 140 (66.4 %) ended up completing the study. Premature withdrawal from the study occurred in 15 of 106 subjects [14.2%] MTS subjects compared to 56 of 105 TS subjects [53.3%]. Lack of efficacy was the primary reason for the high incidence of premature withdrawal from the TS group. Four (4) subjects (3.8%) withdrew from MTS treatment due to AEs compared

with 3 subjects (2.9%) in the TS group. Twenty-three (23; 22 %) subjects in the MTS group and 3 subjects in the TS group (4.5 %) needed dose reductions as a result of AE's. Twenty-nine percent (29 %) in the MTS group had at least once occurrence of patch wear time reduction vs. 4 % in the TS group. In the MTS group, the reasons for discontinuation were pruritus (n=1), anorexia, nervousness, twitching, insomnia (n=1), anorexia, headache, abdominal pain (n=1), and urinary incontinence, anorexia, and weight loss (n=1). In the TS group, reasons for discontinuation were constipation (n=1), rash (n=1) and hypertension (n=1) (Table in Appendix). One serious AE (constipation) occurred in a subject in the TS group (See Safety). The overall incidence of AE's (MTS: 83 %; TS: 55.2 %) and related AE's (MTS: 71.7 %; TS: 17.1 %) were greater in the MTS than in the TS groups. Of the subjects in the MTS group, 62.4% reported at least one AE over a total drug exposure time of 45.1 patient-months compared to 50.5% in the TS group over a total drug exposure time of 45.1 patient-months. The Investigators considered none of the AE's serious (Table-Appendix). Three (3) subjects in the MTS group and 2 in the TS group were withdrawn from the study because of adverse events. The AE's in the MTS group consisted of insomnia (N=2) and depersonalization, hallucinations and manic reaction (N=1), while the AE's in the TS group consisted of headache (N=1) and leg cramps (N=1). A Table of AE's leading to premature discontinuation is provided by the Sponsor and included in the Appendix. The percentage of ITT-S subjects wearing the different patch sizes at the final visit were 6.25 cm 2 (MTS: 2.5, TS: 0), 12.5 cm^2 (MTS: 7.5, TS: 3), 18.75 cm^2 (MTS: 7.5, TS: 18.2), 25 cm^2 (MTS: 52.5, TS: 19.7), 37.5 cm^2 (MTS: 22.5, TS: 31.8) and 50 cm^2 (MTS: 7.5, TS: 27.3), and are indicated in a Table in the Appendix. Patient month drug exposure was greater in the MTS group (76.1 vs. 42.4) as a result of the incidence of TS withdrawals. Mean duration of therapy was slightly greater in the MTS than the TS groups (MTS: 25.9 days; TS: 21.8 days). Mean patch wear time was slightly longer in the TS than in the MTS group at all visits (30-60 minutes).

Results: Treatment with MTS treatment was statistically significant ($p<0.0001$) in the MTS group on the Teacher I/O during week 1 of treatment (Visit 3) and continuing through weeks 2-4 (Visits 4, 5 and 6) (Table and Figure in Appendix). Statistical significance occurred on most of the secondary endpoints (Parent I/O, Teacher OD, Parent OD, Parent O/D, Teacher Abbreviated Conners Rating Scale, Parent Abbreviated Conners Rating Scale, etc).

Conclusion(s): This study showed that in children (ages 6-12 years) with ADHD, MTS was statistically superior to TS (placebo) on the primary and secondary efficacy measures chosen.

D. Efficacy Conclusions

No benefit of MTS over TS (placebo) was demonstrated at doses ranging from 6.25 cm^2-25.0 cm^2 on the Teacher I/O. When the second study used a higher dose [higher starting dose, increased dosing range (6.25 cm^2 – 50 cm^2)] and delayed downward titration, benefit was demonstrated on the Teacher I/O.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

A comparison of the safety profile across the two clinical efficacy studies (Study 010 and 018) raises concerns about the safety of this MTS formulation. In Study 010, the failed efficacy study, the most commonly reported adverse events in the MTS group were anorexia (16.8%), insomnia (16.8%), and headache (13.9%). Clinical efficacy was shown in Study 018 following increased dosing but was offset by a worsening of the adverse event profile [anorexia (50 %), insomnia (30 %) and weight decreases of ≥ 5% (48.6%)]. Use of the transdermal system with MPH (MTS) or without MPH, as in the case of the placebo (TS), both result in dermal irritation (MTS: 88.1%; TS: 66 %), with MTS probably producing sensitization in some subjects.

B. Description of Patient Exposure

The overall extent of exposure to MTS and the TS, control agent, consisted of 706 unique subjects who received at least one application of MTS (2.5 cm^2, 5 cm2, 6.25 cm^2, 10 cm^2, 12.5 cm^2, 20 cm^2, 18.75 cm^2, 25 cm^2, 37.5 cm^2, or 50 cm^2). Of these 706 subjects, 500 were pediatric and 206 were adult subjects. For the phase III controlled trials, 78 % (n=157) of the pediatric subjects received MTS from 21-42 days. For the uncontrolled, long-term pediatric studies, 36 % (n=116) received MTS for more than 120 days. This is summarized in a Table in the Appendix.

C. Methods and Specific Findings of Safety Review

Deaths, Serious Adverse Events, Other Significant Adverse Events

No deaths occurred during any of the studies in the MTS clinical development program. Two SAEs were reported. One SAE (constipation) occurred in a 10-year-old male subject-receiving placebo TS in Study 018. The child had a history of chronic constipation prior to entering the study and 8 days after receiving the TS placebo developed moderate constipation requiring hospitalization. The Investigator felt the SAE was unrelated to study drug. The other SAE occurred in an 8-year-old female subject in Study 021 who became dehydrated. This subject was started on a 12.5 cm^2 MTS patch and 4 days later developed mild anorexia. She remained on that dose for 3 months and underwent an elective outpatient procedure to remove fatty tissue. Post-procedure, the subject began vomiting, reportedly due to an adverse reaction to the anesthesia used for the procedure. She was admitted to the hospital for dehydration later that day and treated with IV fluids and Phenergan. A third SAE is not mentioned in the submission but occurred after the cut-off date

Adverse Events Leading to Discontinuation

There were 21 (3.4 %) adverse events leading to discontinuation in all Studies [MTS: N=21 (3.4 %); TS: N=5 (1.6 %)]. There was nothing unusual with these adverse events. Adverse events in the MTS Group (N=620) consisted of insomnia (N=5; 0.8%), anorexia (N=5; 0.8%), twitching (N=4; 0.6%), hallucinations (N=3; 0.5%), emotional lability (N=2; 0.3%), ET. Al. Adverse events in the TS Group (N=318) consisted of constipation (N=1; 0.3 %), skin rash (N=1; 0.3 %), ET. Al.

In the Phase III Controlled Pediatric Studies, there were 12 (3 %) adverse events leading to discontinuation [MTS: N=7 (3.5 %); TS: N=5 (2.4 %)]. These are identified in a Table in the Appendix identifying Adverse Events Leading to Discontinuation in the Phase III Controlled Trials.

Text Table 8 in the Appendix presents the AEs that occurred at ≥5% frequency in either the MTS or placebo TS treatment groups. Adverse events occurring in a greater percentage of MTS-treated patients than placebo TS-treated patients were application site reaction (MTS: 88.1%; TS: 66 %), anorexia (MTS: 33.7%; TS: 1.9 %), insomnia (MTS: 23.3%; TS: 3.8 %), headache (MTS: 14.4%; TS: 6), Et. Al. Coughing and pharyngitis occurred in a greater percentage of placebo TS-treated patients vs. MTS-treated patients.

The majority of MTS-treated patients reporting anorexia and insomnia were from Study N17-018. The Sponsor performed a post-hoc analysis to understand the higher frequency of adverse events present in this study and stated that the anorexia and insomnia were more likely to occur in stimulant-naïve subjects (39% and 59%, respectively) than in stimulant-experienced patients (19% and 40%, respectively) in the MTS group. Additional analyses for these two events indicated that anorexia resolved for approximately 40% of patients while on the study while 60% had ongoing anorexia at study end. Insomnia resolved for approximately 60% of patients while on the study while 40% had ongoing insomnia at study end. Reducing the patch wear time was effective in ameliorating insomnia. Of 17 patients who had wear time reductions for insomnia, only 6 patients had insomnia at the end of the study. Wear time reduction was not effective in controlling anorexia, however.

Drug-Demographic and Drug-Disease Interactions

In order to address drug-demographic interactions, the Sponsor performed subanalyses of AEs based on selected demographic variables. The number and percent of patients who reported an AE were stratified by gender, race (white, black and other races), ages (6-9 years and 10-12 years) and prior experience with ADHD medication in the Phase III Controlled Pediatric Population. Tables of the Incidence of Adverse Events by Gender and Race in the Phase III Controlled Trials are included in the Appendix. Several of the more commonly observed stimulant-associated side effects (abdominal pain, anorexia and insomnia) were observed more frequently in males and in subjects 6-9 years of age. The frequency of application site reactions was lower in the Black subgroup more than in the White and Other Races subgroups. Overall, the incidence rates for some stimulant-related events in MTS-treated patients who had previous exposure to ADHD medication were appreciably lower than those who had never been treated with ADHD medication as indicated in a table in the Appendix.

Vital Signs in Phase III Controlled Trials (Table-Appendix)

Vital sign data include the systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR) and body weight collected at Baseline and the final visit. The Sponsor used the Wilcoxon Signed-Rank test for within-subject comparison of Baseline values to final values. There were statistically significant changes ($p \leq 0.05$) within the MTS population for SBP (mean increase of 1.3 mmHg), DBP (mean increase of 2.7 mmHg), PR (mean increase of 4.5 bpm), and body weight (mean decrease of

0.9 kg). For the placebo TS population, there was a significant change in body weight (mean increase of 0.5 kg, p ≤0.001).

In the long-term study (011) SBP, DBP, PR and body weight were collected at Baseline and the final visit. The Wilcoxon Signed-Rank test was used for within-subject comparison of Baseline values to final values. There were statistically significant changes observed for DBP (mean increase of 3.0 mmHg, p ≤0.001), PR (mean increase of 3.4 bpm, p ≤0.01), and body weight (mean decrease of 1.0 kg, p ≤0.001).

Pulse Rate (PR)
Heart rates ≥120 bpm were observed in 3 subjects in Study 010 and 7 subjects in Study 018.
In most instances, the reports of rapid heart rate were isolated occurrences of heart rates between 120 and 130 bpm. Subject #06/08 had a heart rate of 132 bpm on Day 21 and subject #14/21 had a heart rate of 136 bpm on Day 22, both subjects were treated with MTS in Study 018. Heart rates ≤50 bpm were observed in 1 subject in Study 010.

Blood Pressure
Episodes of DBP ≥90 mmHg or SBP ≥140 mmHg occurred in 6 subjects in Study 018. Two of these subjects treated with MTS had borderline elevations at Day -1 which persisted during the study (subject #01/01: SBP of 164 mmHg on Day -1 and 140 mmHg on Day 7; subject # 07/15: DBP= 96 mmHg on Day -1 and on Day 27). In the other 4 subjects, the values the values were close to the upper limit values of 90 mmHg and 140 mmHg.

Weight
A significant numbers of children treated with MTS the two Phase III safety efficacy studies and in the long-term study experienced weight loss >5% at some point during the studies. Weight losses ≥5% of Baseline weight were observed in 21 and 54 subjects, respectively in the phase III controlled studies 010 and 018; and 52 subjects in study 011, the long-term study. The 21 subjects in Study 010 consisted of 18 on MTS and 3 on TS (placebo). Three (3) had a weight loss ≥10% (Subject # 11/08: 13.8 % to 5.2 %; Subject # 20/12: 10.6%; and Subject # 20/13: 10.4% and 16.4%). Thirteen (13) subjects in study 011 had a weight loss ≥10%. Subject # 05/09 had the largest weight loss in this study (18 % on day22 and 6.6 % on day 30). The 54 subjects in Study 018 consisted of 51 on MTS and 3 on TS (placebo). Six had a weight loss ≥10% (Subject # 16/04 who concurrently

developed the flu had a 19 % weight decrease with a final MTS dose of 18.75 cm ^{2}).

Laboratory Changes in Phase III Controlled Trials

Laboratory studies included hematology and chemistry collected at Baseline and at the final visit. The Sponsor compared baseline to final values within each treatment group using the Wilcoxon Signed-Rank test (Table-Appendix).

Hematology

Small but statistically significant increases in *hemoglobin and hematocrit* (mean change = +0.17 g/dL, $p \leq 0.001$ and mean change = +0.43%, $p \leq 0.05$, respectively) occurred among MTS, but not placebo treated subjects. No statistically significant changes in *WBC or platelet count* were observed. Within the WBC differential, statistically significant changes for MTS-treated subjects occurred for *neutrophils* (mean change +1.75%, $p \leq 0.05$), *monocytes* (mean change = -0.47%, $p \leq 0.05$), and *eosinophils* (mean change = -0.59%, $p \leq 0.01$); changes seen among placebo-treated subjects were not statistically significant.

In long term Study 011, there was a small, statistically significant decrease in *hematocrit* (mean change = -0.48%, $p \leq 0.05$) was observed. There were no statistically significant changes in hemoglobin or WBC. A mean change in *platelet count* of -10.11 x 103/mm3 from baseline was observed which was statistically significant ($p \leq 0.05$). Statistically significant changes within the WBC differential included decreased *basophils* (mean change = -0.06%, $p \leq 0.01$), decreased *lymphocytes* (mean change = -3.70%, $p \leq 0.001$), and increased *neutrophils* (mean change = +3.87%, $p \leq 0.001$).

Hematology Outliers

- *Hemoglobin/Hematocrit.* Two (2) subjects in Study 018 had clinically significant low values for hemoglobin, hematocrit, or both (anemia) [Subject # 18/01, treated with TS and had a decrease in hemoglobin from 11.2 g/dL to 9.3 g/dL, and a decrease in hematocrit from 35.1% to 28.7% prior to the first dose of study medication; Subject # 18/24, treated with TS had a decrease in hematocrit from 33.6% at Screening to 30.3% on Study Day 29.Neither of these changes were judged to be clinically significant by the Investigator.

- *Platelet.* One (1) subject (# 08/03) on MTS had a platelet value <75,000 cells/mm^3. Baseline *platelet* count was normal

and the final evaluation platelet count was 23,000-cells/ mm^3. The Sponsor states that a normal platelet count was reported on repeat evaluation.

- *Neurtrophil.* One (1) subject in Study 010 and 3 in Study 018 developed neutrophil percents below 20% during treatment. In Study 010, subject # 05/06 (TS) changed from 47.7% (Day 8) to 4.0% (Day 22). In Study 018, subjects # 08/02 (MTS) changed from 49.0% to 19.0%, #09/05 (MTS) changed from 32.0% to 16.0%, and #13/01 (MTS) changed from 60.0% to 18.0%. None of these values were judged clinically significant by the investigator.

- *Eosinophil.* Large numbers of subjects and patients had eosinophil counts >5% at Baseline or during treatment with study medication or both. The highest eosinophil count occurred in Study 011(Subject: #14/06: 18.6% at Baseline; 23.8% at Day 85). The greatest changes in eosinophil counts occurred in Subjects # 19/08 (TS, or, placebo) in Study 010 (15.6% at Baseline to 0.7% at Day 20) and # 20/11 in Study 011 (1.0% at Baseline to 16.2% at Day 101). One subject in Study 010 (# 26/021 MTS) had an eosinophil count judged clinically significant by the investigator (10.4% at screening to 4.6% at Day 25).

Chemistry
Serum chemistry values included Baseline and at the final visit. The Sponsor compared baseline to final values within each treatment group using the Wilcoxon Signed-Rank test (Table-Appendix).

Mean and median changes in serum chemistry values were all small, and similar for MTS-treated and placebo TS-treated patients. Among the MTS subjects, statistically significant changes were observed for *alkaline phosphatase* (mean change = -10.22 U/L, $p \leq 0.001$), *calcium* (mean change = +0.08 mg/dL, $p \leq 0.05$), *creatinine* (mean change = +0.03 mg/dL, $p \leq 0.001$), *phosphates* (mean change = -0.22 mg/dL, $p \leq 0.001$), *SGPT* (mean change = -3.09 U/L, $p \leq 0.001$), *total cholesterol* (mean change = -6.15 mg/dL, $p \leq 0.001$), and *total protein* (mean change = +0.08 g/dL, $p \leq 0.01$). Among the TS group, statistically significant changes occurred for: *albumin* (mean change = -0.09 g/dL, $p \leq 0.001$), *BUN* (mean change = +1.02, $p \leq 0.001$), *phosphates* (mean change = +0.11 mg/dL, $p \leq 0.05$), *SGPT* (mean change = +1.66 U/L,

$p \leq 0.05$), and *total cholesterol* (mean change = -2.81 mg/dL, $p \leq 0.05$).

In the long term Study 011 statistical significance occurred for: *alkaline phosphatase* (mean change = -26.87 U/L, $p \leq 0.001$), *BUN* (mean change = +1.20 mg/dL, $p \leq 0.01$), and *SGPT* (mean change = -1.26 U/L, $p \leq 0.05$).

Chemistry Outliers

- *Liver Function.* Five (5) and two (2) subjects in Studies 010 and 018 had a total bilirubin ≥1.3 mg/dL. In Study 010 and 018, 3 subjects (MTS: 1; TS: 2) who had normal baseline values developed elevated values at Day 22 (1.3-1.6 mg/dL). One subject in Study 010 (# 21/05; MTS) had had Baseline ALT and AST values of 356 U/L and 228 U/L, respectively and Day 17 values of 146 U/L and 102 U/L, respectively.

- *Renal Function.* No pediatric subject had a value of BUN or creatinine above the clinically significant levels during treatment with study medication.

- *Electrolyte.* Clinically significant abnormalities of potassium, sodium, or calcium were observed in 5 subjects in Study 010, 18 subjects in Study 018 and 5 subjects in Study 011.

    - *Potassium* elevations (≥5.5 mmol/L). Two (2) subjects in study 010 [# 05/06, TS; #16/19, MTS] and six (6) subjects in study 018 [# 6/07, TS; # 07/01, MTS; # 10/07, MTS; # 16/11, TS; # 18/07, MTS; and #18/16 [MTS] had normal values at baseline and elevated values at study conclusion. One subject (# 20/12), in Study 011 had a baseline potassium which went from 4.6 mmol/L to 6.6 mmol/L, and which was judged not to be clinically significant.

    - *Sodium.* In study 018, one subject's (#10/16; TS) sodium went from 145 mmol/L at baseline to 156 mmol/L on Day 29; and another subject (#15/02; MTS) the sodium went from 144 mmol/L at baseline to 128 mmol/L on Day 29.

- *Glucose.* Two subjects in study 018 had clinically significant elevated glucose levels (≥160 mg/dL). One subject's (# 03/08; MTS) baseline glucose went from normal at baseline to 184 mg/dL on Day 29. The other subject (# 07/11) only had an elevated baseline value.

Patch Site Assessments

Most studies assessed the skin at the application site for the amount of adhesive residue remaining at the site, discomfort, and evidence of irritation (e.g., erythema and edema).

These components from studies 010 and 018 were reviewed separately by HFD-540, Division of Dermatologic and Dental Drug Products. In addition, Study 008, the skin irritation and sensitization study is reviewed by them. Their conclusions and recommendations are noted below:

"The clinical trials clearly demonstrate that the MTS patch is irritating, and it is suggested that this be reflected in labeling. The results suggest that the adhesive may also cause some irritancy, but not the extent of that observed with the methylphenidate-containing patch.

In the reviewer's assessment, study N17-008 revealed 3 of 99 evaluable subjects (3%) to show reactions suggestive of sensitization in the challenge phase of the study. Generally, a minimum of 200 subjects is suggested to rule out a sensitization rate greater than 1.5%. That a rate of 3% was seen in 99 subjects, suggests that the MTS patch might have some potential to act as a sensitizer. At the very least, seemingly, its role as a sensitizer cannot be excluded. The sensitization issue is further brought into question because, due to irritancy, most subjects may not have been able to be adequately induced because of abbreviated induction periods. No subjects in the MTS placebo arm had reactions suggestive of sensitization.

Photoirritation and photosensitization studies do not appear to have been conducted by the Sponsor, nor was there any discussion found regarding these studies. Generally, such studies can be waived if no components of the study product absorb in the ultraviolet spectrum. With transdermal patches, a Sponsor might support a request for waiver of photosafety studies, by adequately establishing that their product does not transmit ultraviolet light; however, it is noted that the Sponsor describes their product as " [redacted] :" (Volume 3, p. 7). It is acknowledged that the intended site of application(buttocks), is not generally considered a sun-exposed area. However, scenarios could be envisaged that might result in exposure to sun-exposed skin. Given the irritancy of the product, it is possible that some subjects might remove the MTS unit over the course of the day. Alternatively, the patch could fall off. Both scenarios might allow for the potential mishandling of the patch e.g., exposure of product to a body site for which it is unintended (by misapplication), or to other children for whom it is unintended.

The absorption spectrum for the components of the Sponsor's product could not be located by the reviewer, and a response to an inquiry regarding this issue was pending from the assigned chemist at the time of this writing. It is suggested that the Sponsor formally address the issues of photoirritation and photosensitization studies either by requesting a waiver (with scientific rationale) or by conducting the studies.

The pattern of irritancy evidenced in the dermal safety study N17-008, was borne out in the pivotal trials i.e., while the placebo patch was irritating, the methylphenidate containing patch was significantly more so. No new skin-related safety concerns were revealed in the long-term study, N17-021. It is suggested that the exclusion from the pivotal trials of subjects with pre-existing allergies and skin conditions be reflected in labeling".

Special Safety

Study N17-008 assessed the dermal irritation and sensitization potential of MTS in healthy adult subjects. The reader is refereed to the detailed review from HFD-540, Division of Dermatologic and Dental Drug Products, identified under patch site assessments above. In that review, the reviewer concludes that the Sponsor's product is an irritant and that there may be a sensitization issue, "more likely... attributable to the methylphenidate than the adhesives".

Abuse Potential

The Sponsor states that MTS misuse or diversion was not observed during the development program. However, in Study N17-021, there was a substantial number of missing MTS patches for a subject (# 18/16 which the investigator attributed to poor compliance. When multiple MTS were applied to adult stimulant abusers, the reports of dysphoria increased with increased numbers of MTS. The Controlled Substance Staff, HFD-009 evaluated the Sponsor's suggestion that MTS had a lower potential of abuse and diversion than the oral MPH product as a result of its sustained-release formulation. They indicate that MPH from the patch can be easily extracted with common household liquids and organic solvents and be abused. The reader is referred to there review for a complete discussion of these items.

D. Adequacy of Safety Testing

The safety testing as measured by vital signs, weight, height, and laboratory testing was adequate.

E. Summary of Critical Safety Findings and Limitations of Data

The proposed use of this transdermal system formulation will probably result in significant insomnia, anorexia, a weight loss of ≥ 5% of body weight and skin irritation. The impact on long-term development needs to be carefully assessed.

VIII. Dosing, Regimen, and Administration Issues

The reader is referred to OCPB Review dated 03/31/03 for a complete discussion of these issues. OCPB's proposed

recommendations for dosing and administration are included below.

DOSAGE AND ADMINISTRATION

TABLE 3

® System - Recommended Titration Schedule

	Upward Titration, If Response Is Not Maximized		
Week 1	**Week 2**	**Week 3**	**Week 4**
12.5 cm^2 (10 mg / hours)	**18.75 cm^2 (15 mg / hours)**	**25 cm^2 (20 mg / hours)**	**37.5 cm^2 (30 mg / hours)**

Dose/Wear Time Reduction and Discontinuation

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor performed subgroup analyses for individual and grouped studies to examine the relationship between a patient's sex and AE's. The Sponsor states that several of the more commonly observed stimulant-associated side effects (abdominal pain, anorexia and insomnia) were observed more frequently in males and in subject's 6-9 years of age. In Study 018, no significant treatment by gender interaction was found suggesting that the treatment effect was constant over gender categories.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor performed subgroup analyses for individual and grouped studies to examine the relationship between a subjects age and, or, race and the effects on safety and, or, efficacy.

In study 018 the treatment effect was smaller for the 10-13 age group than the 6-9 age group (p=0.06) and smaller for treatment naive patients than for non-naïve patients (p=0.06). However, the treatment was still deemed effective in these groups. In this same study, MTS had no treatment by race interaction effects in reducing Teacher I/O. In Study 010, the statistical review notes that a significant treatment by race interaction. Caucasians (N= 74) benefited most from treatment and Hispanics (N=11) did better on placebo. The Sponsor notes that the frequency of application site reactions was lower in the Black subgroup more than in the White and Other Races subgroups.

The Sponsor states that several of the more commonly observed stimulant-associated side effects (abdominal pain, anorexia and insomnia) were observed in subject's age's 6-9 years of age.

C. Evaluation of Pediatric Program

The pediatric program was adequate as defined by the sponsor conducting two, adequately powered, double blind, placebo controlled trials for Attention Deficit Hyperactivity Disorder (ADHD) in children who are between the ages of 6-12 years.

D. Comments on Data Available or Needed in Other Populations

As requested by HFD-540, the Division of Dermatologic and Dental Drug Products, the Sponsor should "formally address the issues of photoirritation and photosensitization studies either by

requesting a waiver (with scientific rationale) or by conducting the studies".

X. Conclusions and Recommendations

A. Conclusions

- A comparison of the safety profile across the two clinical efficacy studies (Study 010 and 018) raises concerns about the safety of this MTS formulation. In Study 010, the failed efficacy study, the most commonly reported adverse events in the MTS group were anorexia (16.8%), insomnia (16.8%), and headache (13.9%). Clinical efficacy was shown in Study 018 following increased dosing but was offset by a worsening of the adverse event profile [anorexia (50 %), insomnia (30 %) and weight decreases of ≥ 5% (48.6%)]. This safety profile is worse than comparable long acting, oral stimulants (e.g. Concerta, Metadate, Ritalin LA). The *delayed drug absorption, identified in the* PK studies, result in a lack of morning clinical efficacy which can only be overcome by applying a larger dose (as was done in Study 018), and which result in *excessive concentrations and adverse effects late in the day and at night*. Hence, the current formulation impacts safety and the risks associated with its use outweigh any clinical benefit.

- There is excessive *skin irritancy* when using the MTS. In addition, skin *sensitization* is possible. This is not present with the long acting, oral formulations.

- MTS exposure doses are 3.5 fold higher for *d*- methyl-phenidate (*d*-MPH) and 173 fold higher for *l*-methylphenidate (*l*-MPH) as compared to oral administration with Ritalin. The safety profile of MTS is significantly worse than oral MPH suggesting that it cannot be referenced against oral MPH, as is being done in this 505b(2) application. Hence, the question is raised whether there is adequate historical safety information in subjects to adequately assess the safety of *l*-MPH exposure. Hence, a 505b(2) application referenced against Ritalin must be denied[27,28].

[27] Guideline for Industry. The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions.

[28] On 04/19/01, the Agency requested that the Sponsor provide a comparison of d and l enantiomers achieved in animal study's with those in humans to complement the human safety database since humans are exposed to greater levels of the l enantiomers with the patch than the oral dosing. However, Noven felt that the animal studies provided adequate coverage.

- Primary efficacy in 010 and 018 was based on the change from baseline in the Teacher's Inattentive/ Overactivity (I/O) Factor. Since the rating was done at the end of the week based on observations for the last school week, and since the PK studies show delayed absorption during the morning, no statement can be made for clinical evidence of efficacy during the 1-5 hour time interval.

- There exists a real *abuse and, or diversion potential given that the* residual MPH in the patch can be easily extracted.

- Given the PK and the side effect profile there is a real *misuse potential* for off-label uses (e.g. truckers or weight loss).

B. Draft Labeling Review

Since I am not recommending approval for this indication, no labeling review was completed by the undersigned.

C. Recommendations

I recommend that the Division take a non-approvable action for supplement NDA 21-514.

, April 6, 2003
Glenn B. Mannheim, M.D., Date

cc: NDA: 21-514
HFD 120/
AM Homonnay Weikel
G Mannheim
G Dubitsky
P Andreason
T Laughren
R Katz
R Kavanagh
T Massie

XI. Appendix

A. Other Relevant Materials

1. Table: Approximate Incidence Rates for Anorexia and Insomnia Reported with Long-Acting Methylphenidates.

		CONCERTA™ (n=106)	Placebo (n=99)
Concerta™[29]	Anorexia	4%	0%
	Insomnia	4%	1%
		METADATE ® CD (n=188)	**Placebo (n=190)**
Metadate ® CD[30]	Anorexia	9%	2%
	Insomnia	5%	2%
		Ritalin ® LA (n =65)	**Placebo (n =71)**
Ritalin ® LA[31]	Anorexia	2 (3.1)	(0.0)
	Insomnia	2 (3.1)	(0.0)
		[redacted] ® **(n =202)**	**Placebo (n =212)**
[redacted]®[32]	Anorexia	34%	2%
	Insomnia	23 %	4 %

2. Table: Comparison of Select Most Frequently Reported Adverse Events between Studies N17-010 and N17-08

	N17-010 MTS (101)	TS (109)	N17-018 MTS (106)	TS (105)
Anorexia	17 (16.8 %)	2 (1.8 %)	53 (50 %)	2 (1.9 %)
Weight Loss	---	---	11 (10.4 %)	1 (1 %)
Insomnia	17 (16.8 %)	3 (2.8 %)	31 (29.2 %)	5 (4.8 %)
Nervousness	5 (5.0 %)	2 (1.8 %)	11 (10.4 %)	---
Emotional Lability	2 (2 %)	---	12 (11.3 %)	1 (1 %)
Somnolence	---	---	6 (5.7 %)	---
Twitching	3 (3.0 %)	---	7 (6.6 %)	---

[29] Incidence of Treatment-Emergent Events in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA™
[30] Incidence of Treatment-Emergent Events in a Pool of 3-4 Week Clinical Trials of METADATE CD
[31] Treatment-emergent adverse events with an incidence > 2% among Ritalin LA-treated subjects, during the two-week double-blind phase of the clinical study
[32] Adverse Events (Double-Blind Trials)

3. List of Investigators by Study

LIST OF INVESTIGATORS			
Study No.	**Site No.**	**Principal Investigator**	**Address**
N17-002	01	William Pelham, Ph.D.	University at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
N17-003	01	William Pelham, Ph.D.	University at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
N17-004	01	Aziz Laurent, M.D.	PPD Development, Inc. Austin Clinic 706A Ben White Boulevard Austin, Texas 78704
N17-005	01	Michael DePriest, M.D.	ProtoCare Trials, Inc. Las Vegas Center for Clinical Research (LVCCR) 6039 Eldora Avenue Suite H Las Vegas, Nevada 89146
N17-006	01	Ernesto Fuentes, M.D.	South Florida Bioavailability Clinic 11190 Biscayne Boulevard Miami, Florida 33181
N17-007	01	Donald Jasinski, M.D.	Johns Hopkins Bayview Medical Center Mason Lord Building, West Tower, 1st Floor 4940 Eastern Avenue Baltimore, Maryland 21224
N17-008	01	Laurence Galitz, M.D.	South Florida Bioavailability Clinic 11190 Biscayne Boulevard Miami, FL 33181
N17-009	01	William Pelham, Ph.D.	University at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
	02	Michael Manos, Ph.D.	The Cleveland Clinic Foundation Division of Pediatrics, A120 9500 Euclid Avenue Cleveland, Ohio 44195
	03	Cora Ezzell, Ph.D.	Medical University of South Carolina 67 President Street Charleston, South Carolina 29425

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LIST OF INVESTIGATORS			
Study No.	**Site No.**	**Principal Investigator**	**Address**
N17-010 N17-011	01	Daniel Adler, M.D.	Neurology Group of Bergen County, PA 1200 East Ridgewood Avenue 2nd Floor, East Wing Ridgewood, New Jersey 07450
N17-010	02	Gerald August, M.D.	University of Minnesota Department of Psychology 2450 Riverside Avenue Suite F 256/2BW Minneapolis, Minnesota 55454
N17-010	03	Ronald T. Brown, Ph.D.	Medical University of South Carolina (MUSC) Department of Pediatrics 135 Ruteledge Ave PO Box 250561 Charleston, South Carolina 29425
N17-010 N17-011	04	Michael DePriest, M.D.	ProtoCare Trials, Inc. Las Vegas Center for Clinical Research 6039 Eldora Avenue Suite H Las Vegas, Nevada 89146
N17-010 N17-011	05	Michael Duran, M.D.	Oregon Center for Clinical Investigations, Inc. 4309 Oak Ridge Road Lake Oswego, Oregon 97035
N17-010 N17-011	08	James M. Ferguson, M.D.	ProtoCare Trials, Inc. 448 East 6400 South Suite 200 Salt Lake City, Utah 84107
N17-010 N17-011	09	L. Matthew Frank, M.D.	Monarch Research Associates 850 Southampton Avenue, 3rd Floor Norfolk, Virginia 23510
N17-010	25	Laurence Greenhill, M.D.	Columbia University NY State Psychiatric Institute 1051 Riverside Drive New York, New York 10032
N17-010 N17-011	10	James T. Grimm, M.D.	Oregon Center for Clinical Investigations, Inc. 132 East Broadway Street Suite 332 Eugene, Oregon 97401
N17-010 N17-011	11	James A. Hedrick, M.D.	Kentucky Pediatric/Adult Research 201 South 5th Street Suite 102 Bardstown, Kentucky 40004
N17-010 N17-011	12	Saul Helfing, M.D.	Oregon Center for Clinical Investigations 1050 Oak Street SE Suite 3 Salem, Oregon 97309

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LIST OF INVESTIGATORS			
Study No.	**Site No.**	**Principal Investigator**	**Address**
N17-010	13	Diane Johnson, Ph.D.	Duke University Duke Child and Family Study Center 718 Rutherford Street Durham, North Carolina 27705
N17-010 N17-011	14	William Keating, M.D.	SFM Clinical Trials, PC 3730 Scotland Road Scotland, Pennsylvania 17254
N17-010 N17-011	15	Alan Levine, M.D.	Denver Center for Medical Research a Division of Summit Research Network, Inc. 4704 Harlan Street Suite 500 Denver, Colorado 80212
N17-010 N17-011	16	Frank A. Lopez, M.D.	Children's Developmental Center 600 South Orlando Avenue Suite 102 Maitland, Florida 32751
N17-011	17	Michael J. Manos, Ph.D.	The Cleveland Clinic Foundation Division of Ped, A120 9500 Euclid Ave Cleveland, Ohio 44195
N17-010	18	Keith McBurnett, Ph.D.	University of Chicago Child Psychiatry MC 3077 5841 S. Maryland Avenue Chicago, Illinois 60637
N17-010 N17-011	19	Maxine J. Minto, M.D.	Clinical Neuroscience Solutions, PA 77 W. Underwood Street 3rd Floor Orlando, Florida 32806
N17-010	26	Donna Palumbo, Ph.D.	University of Rochester 601 Elmwood Avenue Box 673 Rochester, New York 14642
N17-010 N17-011	20	William Pelham, Ph.D.	State University of New York at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
N17-010 N17-011	21	Ralph W. Richter, M.D.	Clinical Pharmaceutical Trials, Inc. 1705 E. 19th Suite #406 Tulsa, Oklahoma 74104
N17-011	22	Harvey A. Tilker, M.D.	Four Rivers Clinical Research, Inc. 81 Lakeview Drive Paducah, Kentucky 42001

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LIST OF INVESTIGATORS			
Study No.	**Site No.**	**Principal Investigator**	**Address**
N17-011	24	Daniel R. Wynn, M.D.	Consultants in Neurology, Ltd. 1535 Lake Cook Road Suite 601 Northbrook, Illinois 60062
N17-012	01	Donald Jasinski, M.D.	Johns Hopkins Bayview Medical Center Mason Lord Building, West Tower, 1st Floor 4940 Eastern Avenue Baltimore, Maryland 21224
N17-013	01	Daniel R. Wynn, M.D.	Consultants in Neurology, Ltd. 1535 Lake Cook Road Suite 601 Northbrook, Illinois 60062
	02	William Pelham, Ph.D.	University at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
N17-014	01	Mark Allison, M.D.	MDS Pharma Services 4639 South 36th Street Phoenix, Arizona 85040
N17-015	01	William Pelham, Ph.D.	University at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
N17-016	01	Spencer B. Jones, M.D.	Radiant Research, Inc. 420 East South Temple, Suite 200 Salt Lake City, Utah 84111
N17-017	01	Jeffrey Lash, M.D.	DermTech International 15222-B Avenue of Science San Diego, California 92128
N17-018 N17-021	01	Howard Abikoff, Ph.D.	NYU Child Study Center 550 First Avenue New York, NY 10016
N17-018 N17-021	02	Jeffrey T. Apter, M.D.	Princeton Medical Institute 256 Bunn Drive Woodlands Professional Building, Suite 6 Princeton, NJ 08540
N17-018 N17-021	03	Eugene Arnold, M.D.	Ohio State University 1581 Dodd Drive Room 388 Columbus OH 43210-1296
N17-018	05	Joseph Biederman, M.D.	Massachusetts General Hospital ADHD Program 185 Alewife Brook Parkway Suite 2000 Cambridge, Massachusetts 02138

LIST OF INVESTIGATORS			
Study No.	**Site No.**	**Principal Investigator**	**Address**
N17-018 N17-021	06	Oscar G. Bukstein, M.D.	University of Pittsburgh Medical Center Western Psychiatric Institute and Clinic 3811 O'Hara Street Pittsburgh, Pennsylvania 15213-2593
N17-018 N17-021	07	Keith C. Conners, Ph.D.	Duke University Child & Family Study Center Duke University Medical Center 718 Rutherford Street Durham, North Carolina 27705
N17-018 N17-021	08	Daniel Coury, M.D.	Children's Hospital c/o Pediatric Clinical Trials International, Inc. 700 Children's Drive Columbus, Ohio 43205
N17-018 N17-021	09	Michael DePriest, M.D.	ProtoCare Trials, Inc. Las Vegas Center for Clinical Research 6039 Eldora Avenue, Suite H Las Vegas, Nevada 89146-5317
N17-018	10	Michael P. Duran, M.D.	Oregon Center for Clinical Investigations, Inc. 4309 Oak Ridge Road Lake Oswego, Oregon 97035
N17-018 N17-021	11	David Feifel, M.D., Ph.D.	University of California San Diego Medical Center Department of Psychiatry 200 West Arbor Drive San Diego, California 92103-8620
N17-018	12	Giancarlo Ferruzzi, M.D.	Protocare Trials c/o San Antonio Center for Research 8122 Datapoint Drive, Suite 1010 San Antonio, Texas 78229
N17-018 N17-021	13	Laurence Greenhill, M.D.	Columbia University NY State Psychiatric Institute 1051 Riverside Drive New York, New York 10032
N17-018 N17-021	14	James A. Hedrick, M.D.	Kentucky Pediatric/Adult Research 201 South 5th Street Suite 102 Bardstown, Kentucky 40004
N17-018 N17-021	15	Peter Heilbroner, M.D.	Neurology Group of Bergen County PA 1200 East Ridgewood Avenue 2nd Floor East Wing Ridgewood, New Jersey 07450
N17-018 N17-021	16	Saul Helfing, M.D.	Oregon Center for Clinical Investigations 1050 Oak Street SE Suite 3 Salem, Oregon 97309

LIST OF INVESTIGATORS			
Study No.	**Site No.**	**Principal Investigator**	**Address**
N17-018 N17-021	18	Frank A. Lopez, M.D.	Children's Developmental Center 600 South Orlando Avenue Suite 102 Maitland, Florida 32751
N17-018 N17-021	19	William E. Pelham, Ph.D.	University at Buffalo ADHD Program Diefendorf Hall, Room 318 3435 Main Street, Bldg 20 Buffalo, New York 14214-3692
N17-018 N17-021	04	George Realmuto, M.D.	University of Minnesota Medical School Dept. of Psychiatry 2450 Riverside Avenue F256/2B West Building Minneapolis, Minnesota 55454
N17-018 N17-021	20	Ralph W. Richter, M.D.	Clinical Pharmaceutical Trials, Inc. 1705 E. 19th Street Suite #406 Tulsa, Oklahoma 74104
N17-018 N17-021	21	Mark Wolraich, M.D.	Child Study Center 1100 NE 13th Street Oklahoma City, Oklahoma 73117
N17-018 N17-021	22	Daniel R. Wynn, M.D.	Consultants in Neurology, Ltd. 1535 Lake Cook Road Suite 601 Northbrook, Illinois 60062

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4. Summary Tables of Phase III Trials

Text Table 1 Controlled MTS Efficacy Studies in Pediatric Patients with ADHD

Study Number	Study Design/Diagnosis	No. of Subjects/Patients: Gender (M/F) Race (W/B/O)	No. of Subjects/Patients: Mean Age (years) (Range)	No. of Patients Drug/ Daily Dose/ Daily Wear Time	Duration	Primary Efficacy Parameter	Results
Phase III Adequate and Well-Controlled Studies in Community Classroom Setting							
N17-018	Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel-group, flexible dose titration, safety and efficacy study in patients with ADHD	150/61 146/40/25	8.7 (6 – 12)	106 patients: MTS starting at 12.5 cm^2 or 18.75 cm^2 up to 25 cm^2 or 37.5 cm^2 or 50 cm^2 or down to 6.25 cm^2 105 patients: placebo TS ~ 12 hours/day, to be reduced to ~ 7 – 9 hours if side effects warranted	4 weeks	Teacher I/O Factor of IOWA-Conners Rating Scale	MTS highly statistically different from placebo for Teacher I/O and all other teacher and parent ratings ($p<0.0001$). Responder rate was 69% for MTS and 14% for placebo TS ($p<0.0001$).
N17-010	Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel-group, flexible dose titration, safety and efficacy study in patients with ADHD	159/51 152/26/32	8.7 (6 – 12)	101 patients: MTS starting at 6.25 cm^2, up to 12.5 cm^2 or 25 cm^2 109 patients: placebo TS ~ 12 hours/day	3 weeks	Teacher I/O Factor of IOWA-Conners Rating Scale	MTS not statistically different from placebo TS on Teacher I/O or any teacher ratings; parent I/O rating was significant ($p<0.001$). Responder rate was 51% for MTS and 19% for placebo TS ($p<0.0001$).

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5. Pharmacokinetics Studies of Methylphenidate Transdermal System in Humans

Table 1 Pharmacokinetics Studies of Methylphenidate Transdermal System in Humans

Study, Investigators	Study Location	Study Design	Treatment Doses (Formulation)	# Entered/ # Completed	Age Range years	M/F	Duration of Drug Treatment	Results
N17-016, Spencer B. Jones, MD	Radiant Res., Inc., Salt Lake City, UT	open-label, multiple-dose, sequential dose-escalating, 2-period study	37.5 cm^2 MTS applied daily for 4 days, followed by a 50 cm^2 MTS daily for 4 days	12/12	8-16	8/4	8 days total; The daily wear period for each MTS was fixed at either 8 h or 12 h (n = 6 each).	The exposure to *d*-MPH (as measured by C_{max} and AUC_{0-t}) was greater (range, 40 to 60%) after the application of 50 cm^2 MTS compared to 37.5 cm^2 MTS, and T_{max} for *d*-MPH was independent of dose within a given wear period. Similar findings were noted for *l*-MPH.
N17-005, Michael DePriest, MD	Pharmacol Res. Ctr, Las Vegas, NV	open-label, single-dose, randomized, 2-way crossover study	55 mg/25 cm^2 MTS applied to the hip area or the scapular area	27/23	6-12	18/5	16 hours	Both application sites (hip and scapular areas) for the 25 cm^2 MTS resulted in quantifiable plasma levels of *d,l*-MPH. The bioavailability of *d,l*-MPH was ~31% higher following hip application when compared to scapular area. The apparent dose delivered from the 25 cm^2 MTS applied to the hip was ~21% greater than that delivered from the MTS applied to the scapular area
N17-002, William Pelham, PhD, PharmD		Phase II, single-center, double-blind, multiple-dose, randomized, 3-treatment, 3-period, placebo- & active-controlled, crossover	27.4 mg/10 cm^2 MTS delivering 7.5 mg/24 hours applied every 24 h; Ritalin 10 mg TID, placebo MTS	12/9	6-12	9/0	7 days for each treatment	C_{max} of *d*-MPH from two 10 cm^2 MTS units was comparable to 10 mg Ritalin TID. AUC_{∞} of *d*-MPH was higher with two 10 cm^2 MTS units worn 24 hours than from 10 mg Ritalin TID. Both MTS and oral Ritalin produced plasma concentrations of *d*- & *l*-MPH that were lower than the inactive metabolites *d*-RA and *l*-RA. Maximum drug exposure was greater for Ritalin. MTS applied once daily was comparable in efficacy to Ritalin administered three times daily, with both being superior to Placebo
N17-004, Aziz L. Laurent, MD	PPD Development Clin., Austin, TX	open-label, single-dose, 3-way crossover	13.8 mg/6.25 cm^2, 27.5 mg/12.5 cm^2, 55.0 mg/25 cm^2 patch applied to the hip area for 16 hours	14/14	21-39	14/0	16 hours each treatment	AUC and C_{max} for each analyte increased in a dose-dependent manner. T_{max} remained relatively stable across doses within analytes (mean range of 15.60–16.14 hours and 13.49–14.13 hours for *d*- and *l*-MPH, respectively). Mean elimination $t_{1/2}$ from plasma was slightly longer for *d*-MPH (range 3.77-4.47 hours) than *l*-MPH (1.96–2.63 hours). The mean apparent doses for 6.25 cm^2, 12.5 cm^2, and 25 cm^2 MTS were 4.45 mg, 9.14 mg, and 17.61 mg, respectively.
N17-006, Ernesto Fuentes, MD	S. FL BA Clin., Miami, FL	open-label, multiple-dose (steady state), randomized, two-way, crossover	55 mg/25 cm^2 MTS applied to the hip area for 16 hours each day; Ritalin 20 mg TID	30/29	21-40	14/15	Six days each treatment	Daily application of the 25 cm^2 MTS for 6 days resulted in comparable steady-state total exposure (AUC) to *d*-MPH in comparison to repeated 20 mg oral Ritalin TID. However, the two treatments were not bioequivalent based upon mean AUC_{ss} and C_{max} ratios, and their corresponding 90% confidence intervals. Plasma concentrations and exposure to *l*-MPH were much higher following the application of the MTS compared to oral Ritalin
N17-007, Donald Jasinski, MD	Johns Hopkins Bayview Med. Ctr, Baltimore, MD	Part 1: Single-blind, double-dummy, single-dose, dose-rising study of MTS and SC MPH HCl Part 2: Double-blind, triple-dummy, single-dose, randomized, crossover comparison of MTS & SC MPH HCl & oral phentermine	Part 1: 1 to 8 55 mg/25 cm^2 MTS, 25 mg SC MPH HCl & Placebo Part 2: 3 or 6 active MTS (55 mg/25 cm^2), 25, or 50 mg SC MPH HCl, 30 mg oral phentermine & placebo	27 total Part 1 = 7 & Part 2 = 20	31-48	24/3	Six doses (1 day each) in each part.	Exposure to *d*-MPH and *l*-MPH (as measured by C_{max} and AUC_{0-24}) was approximately dose-proportional for MTS and slightly lower than dose-proportional for SC MPH. Variability of C_{max} and AUC for MTS was higher than that following SC administration. The incidence of euphoria and dysphoria was not dose-related for MTS, whereas it was for SC MPH. Blood pressure and heart rate increases from baseline with MTS, MPH SC, and oral phentermine paralleled the rise of MPH or phentermine plasma levels

N17-017, Jeffrey Lash, MD	DermTech Inc., San Diego, CA	open-label, single-dose, randomized, 2-way crossover	55 mg/25 cm^2 MTS to hip for 16 hours	8/8	18-27	8/0	2 treatments six days apart to normal or inflamed skin	With MTS application to inflamed skin, the exposure (as measured by C_{max} and AUC_{0-inf}) to *d,l*-MPH increased 2.5-3-fold compared to intact skin. Application of MTS to injured skin greatly reduced the lag time of *d,l*-MPH appearance in plasma. The apparent dose delivered to inflamed skin was ~2.5-times greater than what was delivered to intact skin. Mean elimination $t_{1/2}$ of *d,l*-MPH was similar for both application conditions of MTS. An increase in the level of *d,l*-MPH was associated with an increase in the mean pulse rate from baseline. There was a linear relationship between apparent dose delivered and C_{max}, as well as with AUC_{0-inf} for MTS application to intact skin.
N17-014, Mark Allison, MD	MDS Pharma Services Phoenix, AZ	open-label	55 mg/25-cm^2 MTS to hip for 16 hours	6/6	19-30	3/3	2 applications of the same patch on consecutive days	MPH concentrations were detectable in plasma by 4 hours following the 1st MTS application. Maximum MPH concentrations were reached 10-18 h following each MTS application. Mean C_{max} values following the 1st & 2nd applications were 11.1 & 6.2 ng/mL, respectively, and 6.0 ng/mL following baseline-adjustment of the 2nd application. Mean MPH AUC_{0-24} values following the 1st & 2nd applications were 147 & 91.1 ng*hr/mL, respectively, and 78.1 ng*hr/mL following baseline-adjustment of the 2nd application. Approximately 62% of the 27.4 mg methylphenidate delivered during the 2 applications was delivered during the 1st application.
N17-012, Donald Jasinski, MD	Johns Hopkins Bayview Med Ctr, Baltimore, MD	Part 1: Double-blind, single-dose, randomized, crossover study of MTS with heat versus no heat. Part 2: Double-blind, single-dose, randomized, placebo-controlled, crossover	Part 1 (Days 1 and 3) 3 55.0 mg/25 cm^2 MTS to one arm, and 3 25 cm^2 placebo MTS to the opposite arm for 8 h; heat applied to right arm. On Days 5 and 7 (Part 2), one 25 cm^2 active or placebo MTS applied to each side of the buccal cavity for 2 hours.	6/6	34-48	5/1	Four treatment periods: 8 hours x 2 days to arm and 2 hours to buccal cavity	Heating the patch delivered ~1.5-fold more drug systemically than application without heat. Application of 2 x 25 cm^2 active MTS to the buccal mucosa provided higher plasma levels of methylphenidate than 3 x 25 cm^2 active MTS through the skin over a shorter wear time. The mean apparent doses delivered from three 55.0 mg/25 cm^2 MTS applied to the arm with and without heat were 48.9 and 32.0 mg, respectively, while that from buccal administration was 61.4 mg. Exaggerated pharmacological effects of methylphenidate (euphoria, dysphoria, increased blood pressure and heart rate) were noted with enhanced absorption of MPH from MTS. First pass metabolism was significantly reduced following application to buccal mucosa compared to oral administration.

6. Uncontrolled, Long-Term, Safety and Efficacy Studies

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Design	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving Each Treatment	Mean Age Yrs (Range)	Gender[a] M/F Race[b] W/B/O	NDA Location
Uncontrolled, long-term, safety and efficacy studies								
N17-011	[redacted] Site 14: W. Keating, MD (Scotland, PA) Site 15: A. Levine, MD (Denver, CO) Site 16: F. Lopez, MD (Maitland, FL) Site 17: M. J. Manos, PhD (Cleveland, OH) Site 19: M. Minto, MD (Orlando, FL) Site 20: W. Pelham, PhD (Buffalo, NY) Site 21: R. Richter, MD (Tulsa, OK) Site 22: H. Tilken, MD (Padukah, KY) Site24: D. Wynn, MD (Northbrook, IL)	Open-label safety and efficacy study in pediatric ADHD patients	Patients began study with MTS 6.25 cm^2 as an initial dose and were titrated between MTS 6.25 cm^2 to 12.5 to 25 cm^2 based on efficacy and tolerance. **MTS wear time:** ≈ 13 hours **Duration:** Three months	First patient enrolled: 17 August 2000 Status: Completed 15 Dec 2000	Total treated: N=118	9.2 (6-13)	94/24 94/11/13	Full Report CRF Tabulations
N17-013	Site 01: D. Wynn, MD (Northbrook, IL) Site 02: W. Pelham, PhD (Buffalo, NY)	Compassionate use in pediatric ADHD patients who participated in Studies N17-011 and N17-015	MTS administered in doses of 6.25, 12.5, 25 cm^2 (for N17-011 patients only), MTS 6.25, 12.5, 25 or 37.5 cm^2 (for N17-015 patients only), with dose titration based on parent and investigator assessment of safety, efficacy and patch tolerability. **MTS wear time:** 12 to 16 hours daily **Duration:** At least nine months (Study N17-015 patients), or until MTS is approved by the FDA and becomes commercially available to the general public (1 to 2 years: Study N17-011 patients)	First patient enrolled: 04 April 2001 Status: Ongoing Data cut-off for NDA: 01 Feb 2002	N=20	9.4 (6-13)	18/2 17/0/3	Full Report N/A CRF Tabulations N/A

N17-021	Site 01: H. Abikoff, PhD (New York, NY) Site 02: J. Apter, MD (Princeton, NJ) Site 03: E. Arnold, MD (Columbus, OH) Site 04: G. Realmuto, MD (Minneapolis, MN) Site 06: O.G. Bukstein, MD (Pittsburgh, PA) Site 07: K. C. Conners, PhD (Durham, NC) Site 08: D. Coury, MD (Columbus, OH) Site 09: M. DePriest, MD (Las Vegas, NV) Site 11: D. Feifel, MD (San Diego, CA) Site 13: L. Greenhill, MD (New York, NY) Site 14: J. Hedtneck, MD (Bardstown, KY) Site 15: P. Heilbronner, MD (Ridgewood, NJ) Site 16: S. Helfing, MD (Salem, OR) Site 18: F. Lopez, MD (Maitland, FL) Site 19: W. Pelham, PhD (Buffalo, NY) Site 20: R. Richter, MD (Tulsa, OK) Site 21: M. Wolraich, MD (Oklahoma City, OK) Site 22: D. R. Wynn, MD	Open-label safety and efficacy study in pediatric ADHD patients who participated in Study N17-018	Patients entered from Study N17-018, and began study with MTS 12.5 cm^2 as an initial dose and were titrated to 6.25, 12.5, 18.75, 25, 37.5 or 50 cm^2 MTS based on efficacy and tolerance over a 3-week period **MTS wear time**: 7 to 12 hours **Duration :** Maximal study participation is about 8 months	First patient enrolled: 16 Nov 2001 Status: Ongoing Data cut-off for NDA: 01 Feb 02	N=63	8.5 16-121	49/14 46/10/7	Full Report N/A CRF Tabulations N/A

7. Phase II Trials

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Design	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving Each Treatment	Mean Age Yrs (Range)	Gender* M/F Race* W/B/O	NDA Location
N17-015	Site 01: W. Pelham, PhD (Buffalo, NY)	Double-blind, randomized, multiple-dose, placebo-controlled, four-treatment, crossover (Part A) or three-treatment, crossover (Part B) safety and efficacy study in pediatric ADHD patients	**Part A:** **Treatment A:** MTS 12.5 cm^2 **Treatment B:** MTS 25 cm^2 **Treatment C:** MTS 37.5 cm^2 **Treatment D:** Placebo TS **Part B:** **Treatment E:** MTS 18.75 cm^2 **Treatment F:** MTS 37.5 cm^2 **Treatment G:** Placebo TS **MTS wear time** Part A: 12 hours amended to 8.5 hours starting at Week 2 Part B: 6 hours **Duration:** Twenty-four treatment days with no washout periods (Part A) and three treatment days (Part B) (total = 27 days)	First patient enrolled: 26 June 2001 Status: Completed 17 August 2001	**Part A:** **Treatment A:** N= 25 **Treatment B:** N=25 **Treatment C:** N=27 **Treatment D:** N=25 **Part B:** **Treatment E:** N=22 **Treatment F:** N=22 **Treatment G:** N=24 Total treated: N=27	9.3 (6-12)	25/2 25/0/2	Full Report CRF Tabulations

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Design	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving Each Treatment	Mean Age Yrs (Range)	Gender* M/F Race* W/B/O	NDA Location
N17-009	Site 01: W. Pelham, PhD (Buffalo, NY) Site 02: M. J. Manos, PhD (Cleveland, OH) Site 03: C. E. Ezzel, PhD (Charleston, SC)	Double-blind, placebo-controlled, randomized, single-dose, 8-way crossover safety and efficacy study in pediatric ADHD patients where the application times differed by 1 hour.	**Treatment A (6 AM application):** MTS 6.25 cm^2 **Treatment B (7 AM application):** MTS 6.25 cm^2 **Treatment C (6 AM application)** MTS 12.5 cm^2 **Treatment D (7 AM application):** MTS 12.5 cm^2 **Treatment E (6 AM application)** MTS 25 cm^2 **Treatment F (7 AM application):** MTS 25 cm^2 **Treatment G (6 AM application).** Placebo TS **Treatment H (7 AM application).** Placebo TS **MTS wear time:** = 13 to 16 hours **Duration:** Eight treatment days with no washout period	First patient enrolled: 26 June 2000 Status: Completed 04 August 2000	**Treatment A:** N=36 **Treatment B:** N=36 **Treatment C:** N=36 **Treatment D:** N=36 **Treatment E:** N=36 **Treatment F:** N=36 **Treatment G:** N=36 **Treatment H:** N=35 Total treated: N=36	9.6 (6-13)	33/3 27/7/2	Full Report CRF Tabulations

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Appendix

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Design	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving Each Treatment	Mean Age Yrs (Range)	Gender[a] M/F Race[b] W/B/O	NDA Location
N17-015	Site 01: W. Pelham, PhD (Buffalo, NY)	Double-blind, randomized, multiple-dose, placebo-controlled, four-treatment, crossover (Part A) or three-treatment, crossover (Part B) safety and efficacy study in pediatric ADHD patients	**Part A:** **Treatment A:** MTS 12.5 cm^2 **Treatment B:** MTS 25 cm^2 **Treatment C:** MTS 37.5 cm^2 **Treatment D:** Placebo TS **Part B:** **Treatment E:** MTS 18.75 cm^2 **Treatment F:** MTS 37.5 cm^2 **Treatment G:** Placebo TS **MTS wear time** Part A: 12 hours amended to 8.5 hours starting at Week 2 Part B: 6 hours **Duration:** Twenty-four treatment days with no washout periods (Part A) and three treatment days (Part B) (total = 27 days)	First patient enrolled: 26 June 2001 Status: Completed 17 August 2001	**Part A:** **Treatment A:** N= 25 **Treatment B:** N=25 **Treatment C:** N=27 **Treatment D:** N=25 **Part B:** **Treatment E:** N=22 **Treatment F:** N=22 **Treatment G:** N=24 Total treated: N=27	9.3 (6-12)	25/2 25/0/2	Full Report CRF Tabulations

8. Ongoing Long-Term Uncontrolled Studies N17-013 & N17-021

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Design	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving MTS	Mean Age Yrs (Range)	Gender[1] M/F Race[2] W/B/O	NDA Location
N17-021	Site 01: H. Abikoff, PhD (New York, NY) Site 02: J. Apter, MD (Princeton, NJ) Site 03: E. Arnold, MD (Columbus, OH) Site 04: G. Realmuto, MD (Minneapolis, MN) Site 06: O.G. Bukstein, MD (Pittsburgh, PA) Site 07: K. C. Conners, PhD (Durham, NC) Site 08: D. Coury, MD (Columbus, OH) Site 09: M. DePriest, MD (Las Vegas, NV) Site 11: D. Feifel, MD (San Diego, CA) Site 13: L. Greenhill, MD (New York, NY) Site 14: J. Hedrick, MD (Bardstown, KY) Site 15: P. Heilbroner, MD (Ridgewood, NJ) Site 16: S. Helfing, MD (Salem, OR) Site 18: F. Lopez, MD (Maitland, FL) Site 19: W. Pelham, PhD (Buffalo, NY) Site 20: R. Richter, MD (Tulsa, OK)	Open-label safety study in pediatric ADHD patients who participated in Study N17-018	Patients entered from Study N17-018, and began study with MTS 12.5 cm^2 as an initial dose and were titrated to 6.25, 12.5, 18.75, 25, 37.5 or 50 cm^2 MTS based on efficacy and tolerance over the initial 3 weeks of treatment. Dosage could be adjusted at any time during the study at the discretion of the Investigator. **MTS wear time**: 7 to 12 hours **Duration :** Maximal study participation is about 22 months with protocol extension	First patient enrolled: 16 Nov 2001 Status Ongoing. Clinical data cut-off: 30 June 2002 (see Section 1.1)	N=189	8.7 (6-12)	135/54 136/30/ 23	Full Report N/A CRF Tabulations N/A

Text Table 2 Ongoing Long-Term Uncontrolled Studies N17-013 & N17-021

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Description	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving MTS	Mean Age Yrs (Range)	Gender[1] M/F Race[2] W/B/O	NDA Location
N17-013	Site 01: D. Wynn, MD (Northbrook, IL) Site 02: W. Pelham, PhD (Buffalo, NY)	Compassionate use in pediatric ADHD patients who participated in Studies N17-011 or N17-015	MTS administered in doses of 6.25, 12.5, and 25 cm^2 (for N17-011 patients only); MTS 6.25, 12.5, 25 and 37.5 cm^2 (for N17-015 patients only), with dose titration based on parent and Investigator assessment of safety, efficacy and patch tolerability. **MTS wear time**: 12 to 16 hours daily **Duration:** Until MTS is approved by the FDA and becomes commercially available to the general public.	First patient enrolled: 04 April 2001 Status: Ongoing. Clinical data cut-off: 30 June 2002	N=20	9.5 (6-13)	18/2 17/0/3	Full Report N/A CRF Tabulations N/A

Study Number	Principal Investigators (only those enrolling patients are listed)	Study Design	Treatment/ Dose/ Duration	Study Status	No. Subjects Receiving MTS	Mean Age Yrs (Range)	Gender[1] M/F Race[2] W/B/O	NDA Location
	Site 21: M. Wolraich, MD (Oklahoma City, OK) Site 22: D. R. Wynn, MD (Northbrook, IL)							

9. N17-010: Baseline Demographic Characteristics

Table 14. Baseline Demographic Characteristics – Intent-to-Treat Patients

Demographic Characteristic	MTS (n=101)	TS (n=109)	p-value[a]	Total (n=210)
Age (yr)				
Mean	8.7	8.6		8.7
s.d.	1.7	1.6		1.7
Median	9.0	8.0		8.0
Minimum	6	6		6
Maximum	12	12	0.9274	12
Age Distribution, n (%)				
6 – 8 yr	50 (49.5)	58 (53.2)		108 (51.4)
9 – 10 yr	34 (33.7)	36 (33.0)		70 (33.3)
11 – 12 yr	17 (16.8)	15 (13.8)	0.8614	32 (15.2)
Age at ADHD Onset (yr)				
Mean	5.5	5.7		5.6
s.d.	1.8	2.0		1.9
Median	5.0	5.0		5.0
Minimum	1	<1		<1
Maximum	11	12	0.8090	12
Sex, n (%)				
Male	75 (74.3)	84 (77.1)		159 (75.7)
Female	26 (25.7)	25 (22.9)	0.6858	51 (24.3)
Ethnic Background, n (%)				
Caucasian	76 (75.2)	76 (69.7)		152 (72.4)
African-American	9 (8.9)	17 (15.6)		26 (12.4)
Asian	1 (1.0)	0 (0.0)		1 (0.5)
Hispanic	11 (10.9)	11 (10.1)		22 (10.5)
Other	4 (4.0)	5 (4.6)	0.5948	9 (4.3)
IQ				
N	101	108		209
Mean	103.4	101.1		102.2
s.d.	15.7	15.9		15.8
Median	103.0	100.0		101.0
Minimum	71	73		71
Maximum	142	146	0.3073	146
Subtype of ADHD[b], n (%)				
Inattentive	10 (9.9)	16 (14.7)		26 (12.4)
Hyperactive/Impulsive	2 (2.0)	5 (4.6)		7 (3.3)
Combined (Inattentive & Hyperactive/Impulsive)	89 (88.1)	88 (80.7)	0.5935	177 (84.3)

Demographic Characteristic	MTS (n=101)	TS (n=109)	p-value[a]	Total (n=210)
Comorbid Behavior Disorders[b], n (%)				
ODD	38 (37.6)	39 (35.8)		77 (36.7)
CD	1 (1.0)	0 (0.0)		1 (0.5)
Combined (ODD/CD)	25 (24.8)	20 (18.3)		45 (21.4)
Did Not Meet Criteria	37 (36.6)	50 (45.9)	0.3821	87 (41.4)
CGI Severity of Illness[c], n (%)				
Not Assessed	1 (1.0)	0 (0.0)		1 (0.5)
Mildly ill	2 (2.0)	5 (4.6)		7 (3.3)
Moderately ill	63 (62.4)	66 (60.6)		129 (61.4)
Markedly ill	28 (27.7)	34 (31.2)		62 (29.5)
Severely ill	7 (6.9)	4 (3.7)	0.4521	11 (5.2)
Teacher I/O Factor				
N	98	103		201
Mean	9.5	9.4		9.4
s.d.	3.93	3.78		3.85
Median	10.0	10.0		10.0
Minimum	1.0	0.0		0.0
Maximum	15.0	15.0	0.6887	15.0

a: p-Values were based on ANOVA (continuous data) and Cochran-Mantel-Haenszel test (categorical data), with treatment group and center main effects, and treatment group-by-center interactive effects. The p-values for the Teacher I/O Factor were based on two-way ANOVA models that included treatment group and center main effects and treatment group-by-center interaction effects.

b: ADHD subtypes and comorbid behavior disorders were based on teacher and parent DBD Rating Scales.

c: No patients were rated "Normal, not at all ill," Borderline mentally ill," or "Among the most extremely ill."

10. N17-018: Baseline Demographic Characteristics

Table 7 Baseline Demographic and Physical Characteristics (ITT Population)

Demographic Characteristic	Treatment Group MTS (n=106)	Treatment Group TS (n=105)	p-value	Total (n=211)
Age (yr):				
N	106	105		211
Mean	8.5	8.8		8.7
s.d.	1.8	1.8		1.8
Median	8.0	9.0		9.0
Minimum	6	6		6
Maximum	12	12	0.2046	12
Age Distribution (yr)				
< 6	0 (0.0%)	0 (0.0%)		0 (0.0%)
6 – 8	57 (53.8%)	44(41.9%)		101 (47.9%)
9 – 10	27 (25.5%)	41 (39.0%)		68 (32.2%)
11 – 12	22 (20.8%)	20 (19.0%)		42 (19.9%)
> 12	0 (0.0%)	0 (0.0%)	0.0943	0 (0.0%)
Age at ADHD Onset				
N	106	105		211
Mean	5.2	5.3		5.3
s.d.	1.8	1.9		1.8
Median	5.0	5.0		5.0
Minimum	1	2		1
Maximum	12	12	0.7860	12
Gender				
Male	74 (69.8%)	76 (72.4%)		150 (71.1%)
Female	32 (30.2%)	29 (27.6%)	0.6170	61 (28.9%)
Race				
Caucasian	72 (67.9%)	74 (70.5%)		146 (69.2%)
African-American	20 (18.9%)	20 (19.0%)		40 (19.0%)
Asian	0 (0.0%)	1 (1.0%)		1 (0.5%)
Hispanic	8 (7.5%)	6 (5.7%)		14 (6.6%)
Other*	6 (5.7%)	4 (3.8%)	0.7349	10 (4.7%)
Weight (lb):				
N	105	104		209
Mean	72.7	76.6		74.7
s.d.	26.5	28.0		27.3
Median	68.0	68.5		68.0
Minimum	37	43		37
Maximum	205	172	0.3059	205
Height (in):				
N	105	104		209
Mean	52.4	53.6		53.0
s.d.	5.1	4.9		5.0
Median	51.5	53.5		53.0
Minimum	43.0	41.0		41.0
Maximum	66.1	66.9	0.0880	66.9

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Demographic Characteristic	Treatment Group: MTS (n=106)	Treatment Group: TS (n=105)	p-value	Total (n=211)
Body Temperature (F)				
N	105	104		209
Mean	98.0	97.9		97.9
s.d.	1.0	1.1		1.1
Median	98.1	97.9		97.9
Minimum	95.3	93.0		93.0
Maximum	100.4	100.0	0.6040	100.4
IQ				
N	106	105		211
Mean	102.3	98.8		100.6
s.d.	16.7	14.2		15.6
Median	100.5	99.0		99.0
Minimum	70	71		70
Maximum	151	137	0.1044	151
Subtype of ADHD				
Inattentive	11 (10.4%)	14 (13.3%)		25 (11.8%)
Hyperactive/Impulsive	2 (1.9%)	2 (1.9%)		4 (1.9%)
Combined (Inattentive and Hyperactive/Impulsive)	93 (87.7%)	89 (84.8)	0.9116	182 (86.3%)
Comorbid Behavior Disorders:				
Oppositional Defiant Disorder	43 (40.6%)	31 (29.5%)		74 (35.1%)
Conduct Disorder	1 (0.9%)	1 (1.0%)		2 (0.9%)
Combined (Oppositional Defiant Disorder/Conduct Disorder)	25 (23.6%)	26 (24.8%)	0.5261	51 (24.2%)
Did Not Meet Criteria	37 (34.9%)	47 (44.8%)		84 (39.8%)
CGI Severity of Illness:				
Normal, not at all ill	0 (0.0%)	0 (0.0%)		0 (0.0%)
Borderline mentally ill	0 (0.0%)	0 (0.0%)		0 (0.0%)
Mildly ill	0 (0.0%)	2 (1.9%)		2 (0.9%)
Moderately ill	57 (53.8%)	54 (51.4%)		111 (52.6%)
Markedly ill	35 (33.0%)	36 (34.3%)		71 (33.6%)
Severely ill	12 (11.3%)	11 (10.5%)		23 (10.9%)
Among the most extremely ill	1 (0.9%)	0 (0.0%)	0.6781	1 (0.5%)
Not Assessed	0 (0.0%)	0 (0.0%)		0 (0.0%)
Missing	1 (0.9%)	2 (1.9%)		3 (1.4%)

Data Source: Section 15, Source Table 15.2.1 and Appendix 16.2, Listing 16.2.1.2
ADHD subtypes were based on the teacher and parent DBD Rating Scales.
p-values between treatment groups were based on one-way ANOVA (continuous data) and CMH (categorical data).
*Other included 10 cases of multiracial or multiethnic.

11. Incidence of Adverse Events (≥ 5%) in Either Treatment Group by Preferred COSTART Term within Body System-Phase III Controlled Pediatric Population, n (%)

Text Table 8 Incidence of Adverse Events (≥5%) in Either Treatment Group by Preferred COSTART Term within Body System-Phase III Controlled Pediatric Population, n (%)

Body System/COSTART Term	MTS (n=202)	Placebo TS (n=212)
Number of Patients with Any Adverse Event	190 (94.1)	169 (79.7)
Body as a Whole		
Headache	29 (14.4)	13 (6.1)
Abdominal pain	27 (13.4)	12 (5.7)
Viral infection	14 (6.9)	12 (5.7)
Digestive System		
Anorexia	68 (33.7)	4 (1.9)
Vomiting	10 (5.0)	9 (4.2)
Metabolic/Nutritional		
Weight loss	11 (5.4)	1 (0.5)
Nervous System		
Insomnia	47 (23.3)	8 (3.8)
Nervousness	16 (7.9)	2 (0.9)
Emotional lability	14 (6.9)	1 (0.5)
Twitching	10 (5.0)	0 (0.0)
Respiratory System		
Cough increased	11 (5.4)	16 (7.5)
Rhinitis	11 (5.4)	11 (5.2)
Pharyngitis	7 (3.5)	15 (7.1)
Skin and Appendages		
Application site reaction	178 (88.1)	140 (66.0)

Data Source: Table 5.1 in Section 19

12. Adverse Events Leading to Discontinuation in the Phase III Controlled Pediatric Trials

Table 5.31
Adverse Events which Led to Discontinuation by Preferred COSTART Term within Body System
Safety Population - Phase III Controlled Pediatric Studies

Body System/ COSTART Term	MTS (N=202)	PLACEBO (N=212)	TOTAL (N=406)
Number with Any Adverse Event	7 (3.5%)	5 (2.4%)	12 (3.0%)
NERVOUS SYSTEM	4 (2.0%)	0	4 (1.0%)
INSOMNIA	3 (1.5%)	0	3 (0.7%)
DEPERSONALIZATION	1 (0.5%)	0	1 (0.2%)
HALLUCINATIONS	1 (0.5%)	0	1 (0.2%)
MANIC REACTION	1 (0.5%)	0	1 (0.2%)
NERVOUSNESS	1 (0.5%)	0	1 (0.2%)
TWITCHING	1 (0.5%)	0	1 (0.2%)
DIGESTIVE SYSTEM	3 (1.5%)	1 (0.5%)	4 (1.0%)
ANOREXIA	3 (1.5%)	0	3 (0.7%)
CONSTIPATION	0	1 (0.5%)	1 (0.2%)
BODY AS A WHOLE	1 (0.5%)	1 (0.5%)	2 (0.5%)
ABDOMINAL PAIN	1 (0.5%)	0	1 (0.2%)
HEADACHE	1 (0.5%)	1 (0.5%)	2 (0.5%)
METABOLIC/NUTRITIONAL	1 (0.5%)	0	1 (0.2%)
WEIGHT LOSS	1 (0.5%)	0	1 (0.2%)

Notes:
1. The N in the column title represents the number of treated subjects/patients, and is used to calculate percentages.
2. Subjects/patients are counted only once at the body system level, even if they have multiple preferred terms within the body system.
3. Subjects/patients with multiple occurrences of the same preferred term are counted only once within a treatment column, even if that treatment occurred in multiple crossover periods, or in multiple studies.
4. Subjects/patients with multiple occurrences of the same preferred term on different treatments are counted only once in the TOTAL column.
5. Includes Study Number(s) N17-010 and N17-018.

Body System/ COSTART Term	MTS (N=202)	PLACEBO (N=212)	TOTAL (N=406)
SKIN AND APPENDAGES	1 (0.5%)	1 (0.5%)	2 (0.5%)
PRURITUS	1 (0.5%)	0	1 (0.2%)
RASH	0	1 (0.5%)	1 (0.2%)
UROGENITAL SYSTEM	1 (0.5%)	0	1 (0.2%)
URINARY INCONTINENCE	1 (0.5%)	0	1 (0.2%)
CARDIOVASCULAR	0	1 (0.5%)	1 (0.2%)
HYPERTENSION	0	1 (0.5%)	1 (0.2%)
MUSCULO-SKELETAL	0	1 (0.5%)	1 (0.2%)
LEG CRAMPS	0	1 (0.5%)	1 (0.2%)

CLINICAL REVIEW
Appendix

13. Incidence of Incidence of Adverse Events by Gender-Phase III Controlled Trials

Text Table 12 Incidence of Adverse Events by Gender[1]-Phase III Controlled Pediatric Population, n (%)

	MTS (n=202)		Placebo TS (n=212)	
Body System/COSTART Term	**Males (n=145)**	**Females (n=57)**	**Males (n=158)**	**Females (n=54)**
Number of Patients with Any Adverse Event	138 (95.2)	52 (91.2)	124 (78.5)	45 (83.3)
Body as a Whole				
Abdominal pain	22 (15.2)	5 (8.8)	11 (7.0)	1 (1.9)
Digestive System				
Anorexia	52 (35.9)	16 (28.1)	4 (2.5)	0 (0.0)
Nervous System				
Insomnia	36 (24.8)	11 (19.3)	6 (3.8)	2 (3.7)
Nervousness	8 (5.5)	8 (14.0)	1 (0.6)	1 (1.9)

[1] ≥5% difference between males and females.

Data Source: Tables 5.7 and 5.8 in Section 19

14. Adverse Events by Race-Phase III Controlled Trials

Text Table 13 Incidence of Adverse Events by Race[1]-Phase III Controlled Pediatric Population, n (%)

	MTS (n=202)			Placebo TS (n=212)		
Body System/COSTART Term	**White (n=145)**	**Black (n=28)**	**Other Races (n=29)**	**White (n=149)**	**Black (n=37)**	**Other Races (n=26)**
Number of Patients with Any Adverse Event	138 (95.2)	25 (89.3)	27 (93.1)	126 (84.6)	23 (62.2)	20 (76.9)
Body as a Whole						
Abdominal pain	18 (12.4)	5 (17.9)	4 (13.8)	8 (5.4)	3 (8.1)	1 (3.8)
Headache	19 (13.1)	6 (21.4)	4 (13.8)	10 (6.7)	3 (8.1)	0 (0.0)
Viral infection	13 (9.0)	1 (3.6)	0 (0.0)	10 (6.7)	1 (2.7)	1 (3.8)
Digestive System						
Anorexia	52 (35.9)	9 (32.1)	7 (24.1)	2 (1.3)	2 (5.4)	0 (0.0)
Nervous System						
Insomnia	40 (27.6)	5 (17.9)	2 (6.9)	6 (4.0)	1 (2.7)	1 (3.8)
Somnolence	3 (2.1)	3 (10.7)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory System						
Cough increased	7 (4.8)	4 (14.3)	0 (0.0)	10 (6.7)	1 (2.7)	5 (19.2)
Rhinitis	10 (6.9)	1 (3.6)	0 (0.0)	7 (4.7)	1 (2.7)	3 (11.5)
Skin and Appendages						
Application site reaction	135 (93.1)	16 (57.1)	27 (93.1)	106 (71.1)	15 (40.5)	19 (73.1)

[1] ≥5% difference among Whites, Blacks, and Other races.

Data Source: Tables 5.9, 5.10, and 5.11 in Section 19

15. Stimulant Associatedn Adverse Event by Prior Experience with ADHD Medications in Phase III Coantrolled Trials

Text Table 31 Stimulant-Associated Adverse Events by Prior Experience with ADHD Medication-Phase III Controlled Pediatric Population, n (%)

	MTS	
AE	**With Prior ADHD Medication (n=93)**	**Without Prior ADHD Medication (n=109)**
Anorexia	25 (26.9)	43 (39.4)
Insomnia	11 (11.8)	36 (33.0)
Headache	10 (10.8)	19 (17.4)
Abdominal pain	7 (7.5)	20 (18.3)

Data Source: Tables 5.14 and 5.15 in Section 19

16. Vital Signs Data in Phase III Controlled Studies: Systolic Blood Pressure, Diastolic Blood Pressure, Pulse, Body Weight

Table 7.0
Vital Signs Data: Baseline, Final and Change from Baseline
Safety Population - Phase III Controlled Pediatric Studies

	MTS	Placebo Only	Total
Systolic Blood Pressure (mm Hg)			
Baseline			
N	206	214	420
Mean	104.3	104.6	104.5
Standard Deviation	10.1	10.3	10.2
Median	102.5	103.0	103.0
Min - Max	81 - 166	78 - 142	78 - 166
Final			
N	201	199	400
Mean	105.4	102.7	104.6
Standard Deviation	8.9	9.7	9.4
Median	104.0	105.0	104.0
Min - Max	86 - 132	80 - 135	80 - 135
Change From Baseline			
N	200	199	399
Mean	1.3	-1.8	0.2
Standard Deviation	9.8	10.3	10.1
Median	0.5	0.0	0.0
Min - Max	-34 - 27	-45 - 28	-45 - 28
P-Value [1]	0.050	0.240	0.866

[1] The Wilcoxon Signed-Rank Test is used for within patient comparisons of baseline to final.

Includes Study Number(s) N17-010 and N17-018.

	MTS	Placebo Only	Total
Diastolic Blood Pressure (mm Hg)			
Baseline			
N	206	214	420
Mean	64.1	64.7	64.4
Standard Deviation	8.0	8.3	8.2
Median	63.0	64.0	64.0
Min - Max	47 - 85	48 - 90	47 - 90
Final			
N	201	199	400
Mean	66.9	64.3	65.6
Standard Deviation	8.5	8.6	8.7
Median	66.0	63.0	64.0
Min - Max	40 - 96	46 - 88	40 - 96
Change From Baseline			
N	200	199	399
Mean	2.7	-0.6	1.0
Standard Deviation	9.9	8.3	9.3
Median	2.0	0.0	0.0
Min - Max	-32 - 38	-26 - 29	-32 - 38
P-Value [1]	<0.001	0.369	0.030

[1] The Wilcoxon Signed-Rank Test is used for within patient comparisons of baseline to final.

Study 010: Disposition of Treated Subjects

Table 11. Disposition of Treated Patients – Intent-to-Treat Patients (n, %)

	MTS (n=101)	TS (n=109)	Total (n=210)
Patients Evaluated for:			
Adverse Events	101 (100)	109 (100)	210 (100)
Routine Laboratories	93 (92.1)	96 (88.1)	189 (90.0)
Efficacy			
Intent-to-Treat (ITT-E)	101 (100)	108 (99.1)	209 (99.5)
Per Protocol (PPE)	91 (90.1)	95 (87.2)	186 (88.6)
Patient Completion Status:			
Completed All Visits	92 (91.1)	97 (89.0)	189 (90.0)
Discontinued Due to:	9 (8.9)	12 (11.0)	21 (10.0)
Adverse Event	3 (3.0)	2 (1.8)	5 (2.4)
Protocol Violation[a]	2 (2.0)	3 (2.8)	5 (2.4)
Administrative	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	1 (1.0)	6 (5.5)	7 (3.3)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (3.0)	1 (0.9)	4 (1.9)

a: These patients are identified in Section 10.2.

Study 010: Summary of Duration of Exposure: ITT and PPE

Table 39. Summary of Duration of Therapy – Intent-to-Treat Patients and Per Protocol Efficacy Patients

	MTS	TS	Total
ITT Patients			
N	101	109	210
Duration of Therapy (Days)			
Mean	20.5	21.1	20.8
s.d.	5.3	5.0	5.2
Median	21	21	21
Minimum	2	5	2
Maximum	33	42	42
Distribution of Days of Therapy, n (%)			
1 – 10	3 (3.0)	5 (4.6)	8 (3.8)
11 – 17	10 (9.9)	11 (10.1)	21 (10.0)
18 – 29	85 (84.2)	91 (83.5)	176 (83.8)
> 29	3 (3.0)	2 (1.8)	5 (2.4)
Per Protocol Efficacy Patients			
N	91	95	186
Duration of Therapy (Days)			
Mean	21.2	20.8	21.0
s.d.	4.5	4.4	4.5
Median	21	21	21
Minimum	2	5	2
Maximum	33	29	33
Distribution of Days of Therapy, n (%)			
1 – 10	3 (3.3)	2 (2.1)	5 (2.7)
11 – 17	9 (9.9)	7 (7.4)	16 (8.6)
18 – 29	79 (86.8)	84 (88.4)	163 (87.6)
> 29	0 (0.0)	2 (2.1)	2 (1.1)

Cross-reference: Appendix Table 14.4.5 and Appendix Listing 16.4.5 and 16.4.6.

CLINICAL REVIEW
Appendix

Study 010: Summary of Patch Size Distribution by Visit-ITT

Table 41. Summary of Patch Size Distribution by Scheduled Visit Day – Intent-to-Treat Patients (n, %)

Patch Size Category[a]	MTS (n=101)	TS (n=109)	Total (n=210)
Visit 3 (Day 7)			
N	99	105	204
Unknown	2 (2.0)	4 (3.8)	6 (2.9)
6.25 cm^2	83 (83.8)	80 (76.2)	163 (79.9)
12.5 cm^2	14 (14.1)	21 (20.0)	35 (17.2)
25 cm^2	0 (0.0)	0 (0.0)	0 (0.0)
Visit 4 (Day 14)			
N	97	103	200
Unknown	3 (3.1)	7 (6.8)	10 (5.0)
6.25 cm^2	13 (13.4)	12 (11.7)	25 (12.5)
12.5 cm^2	71 (73.2)	63 (61.2)	134 (67.0)
25 cm^2	10 (10.3)	21 (20.4)	31 (15.5)
Visit 5 (Day 21)			
N	71	80	151
Unknown	2 (2.8)	2 (2.5)	4 (2.7)
6.25 cm^2	6 (8.5)	4 (5.0)	10 (6.6)
12.5 cm^2	25 (35.2)	13 (16.3)	38 (25.2)
25 cm^2	38 (53.5)	61 (76.3)	99 (65.6)
Final Visit (LOCF)			
N	101	109	210
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
6.25 cm^2	9 (8.9)	11 (10.1)	20 (9.5)
12.5 cm^2	25 (24.8)	13 (11.9)	38 (18.1)
25 cm^2	67 (66.3)	85 (78.0)	152 (72.4)

a: Distributions were based on the patch size worn on the scheduled visit day not necessarily the actual visit day.

Cross-reference: Appendix Table 4.4.6.2 and Appendix Listing 16.4.5 and 16.4.6.

Study 010: Summary of Tolerability: ITT

Table 45. Overall Summary of Tolerability – Intent-to-Treat Patients

Category	MTS (n=101)	TS (n=109)	Total (n=210)
Total Patient-Months of Drug Exposure	45.1	37.1	82.2
Number (%) of Patients With Adverse Events[a]	63 (62.4)	55 (50.5)	118 (56.2)
Total Number of Adverse Events	142	108	250
Number (%) of Patients With Serious Adverse Events[a]	0 (0.0)	0 (0.0)	0 (0.0)
Number (%) of Patients Requiring Patch Size Reduction Due to AE(s)	5 (5.0)	0 (0.0)	5 (2.4)
Number (%) of Patients With Study Medication Permanently Discontinued Due to AE	3 (3.0)	2 (1.8)	5 (2.4)
Number (%) of Patients With Study Medication Temporarily Discontinued Due to AE	3 (3.0)	1 (0.9)	4 (1.9)
Number (%) of Deaths	0 (0.0)	0 (0.0)	0 (0.0)

a: Non-serious adverse events were counted up to 2 days after last patch application; serious adverse events were counted up to 30 days after last patch application.

Study 010: Summary of AE's Leading to Premature Termination-ITT

Table 50. Summary of Adverse Events Leading to Premature Termination – Intent-to-treat Patients (n, %)

Body System[a] Preferred Term[b]	MTS (n=101)	TS (n=109)	Total[c] (n=210)
Patients With Study Medication Permanently Discontinued Due To AE	3 (3.0)	2 (1.8)	5 (2.4)
Body As A Whole	---	**1 (0.9)**	**1 (0.5)**
Headache	---	1 (0.9)	1 (0.5)
Musculoskeletal System	---	**1 (0.9)**	**1 (0.5)**
Leg Cramps	---	1 (0.9)	1 (0.5)
Nervous System	**3 (3.0)**	---	**3 (1.4)**
Depersonalization	1 (1.0)	---	1 (0.5)
Hallucinations	1 (1.0)	---	1 (0.5)
Insomnia	2 (2.0)	---	2 (1.0)
Manic Reaction	1 (1.0)	---	1 (0.5)

NOTE: "---" indicates that the number and percent of patients equals 0 (0.0).

a: A patient who experienced more than one type of adverse event within the same body system is counted once at the body system level. A patient who experienced more than one episode of the same adverse event is counted once at the preferred term level.

b: All events resolved following discontinuation of MTS.

c: One patient had Depersonalization, Hallucinations, and Manic Reaction.

Study 018: Final Disposition-ITT

Table 6 Patient Accounting and Final Disposition

Patient Accounting	Treatment Group MTS	TS	Total
Number of Patients:			
Screened			268
Screen Failures			56
Randomized	106*	106*	212
Treated	106	105†	211
Patients Evaluated for:			
Adverse Events	106 (100.0%)	105 (100.0%)	211 (100.0%)
Routine Laboratories	104 (98.1%)	100 (95.2%)	204 (96.7%)
Efficacy			
Intent-to-Treat	103 (97.2%)	104 (99.0%)	207 (98.1%)
Patient Completion Status:			
Completed all Visits	91 (85.8%)	49 (46.7%)	140 (66.4%)
Discontinued Due to:	15 (14.2%)	56 (53.3%)	71 (33.6%)
Adverse Event	4 (3.8%)	3 (2.9%)	7 (3.3%)
Protocol Violation	2 (1.9%)	0 (0.0%)	2 (0.9%)
Administrative	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	8 (7.5%)	49 (46.7%)	57 (27.0%)
Lost to Follow-up	0 (0.0%)	1 (1.0%)	1 (0.5%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other[‡]	1 (0.9%)	3 (2.9%)	4 (1.9%)

Data Source: Section 15, Source Table 15.1.1 and Appendix 16.2, Listing 16.2.1.1

Screened Patients gave informed written consent.

Treated Patients received at least one dose of study medication.

Patients evaluated for intent-to-treat efficacy were patients who had at least one post-baseline efficacy evaluation.

Percents for evaluation groups were based on the total number of patients treated.

Percents for patient completion status were based on the total number of treated patients.

* Because of a site error, Patient 19006, initially assigned to TS, was inadvertently given MTS at Visit 3, after 1 week of treatment, whereas Patient 19007, initially assigned to MTS, was inadvertently given TS at Visit 3. Both patients were included in all safety and efficacy analyses as MTS patients.

† Patient 20006 was lost to follow-up and was never treated, hence this patient was not included in any analysis.

‡ Other included 2 cases (16/22 and 16/25 both TS) of the parent having withdrawn consent; 1 case (13/02 MTS) of the patient never returning (lost to follow-up), and 1 case (14/13 TS) of the patient enrolling in study N17-021 because of lack of efficacy in N17-018.

Study 018: AE's Leading to Discontinuation (ITT-S)

Table 19 Adverse Events Leading to Discontinuation of Treatment (ITT-S Population)

Treated Patients	Treatment Group MTS (n=106)	TS (n=105)	Total (n=211)
Patients with Study Medication Permanently Discontinued due to AE (s)	4 (3.8%)	3 (2.9%)	7 (3.3%)
Body System/ PREFERRED TERM			
Body as a Whole	1 (0.9%)	0 (0.0%)	1 (0.5%)
ABDOMINAL PAIN	1 (0.9%)	0 (0.0%)	1 (0.5%)
HEADACHE	1 (0.9%)	0 (0.0%)	1 (0.5%)
Cardiovascular System	0 (0.0%)	1 (1.0%)	1 (0.5%)
HYPERTENSION	0 (0.0%)	1 (1.0%)	1 (0.5%)
Digestive System	3 (2.8%)	1 (1.0%)	4 (1.9%)
ANOREXIA	3 (2.8%)	0 (0.0%)	3 (1.4%)
CONSTIPATION	0 (0.0%)	1 (1.0%)	1 (0.5%)
Metabolic and Nutritional Disorders	1 (0.9%)	0 (0.0%)	1 (0.5%)
WEIGHT LOSS	1 (0.9%)	0 (0.0%)	1 (0.5%)
Nervous System	1 (0.9%)	0 (0.0%)	1 (0.5%)
INSOMNIA	1 (0.9%)	0 (0.0%)	1 (0.5%)
NERVOUSNESS	1 (0.9%)	0 (0.0%)	1 (0.5%)
TWITCHING	1 (0.9%)	0 (0.0%)	1 (0.5%)
Skin and Appendages	1 (0.9%)	1 (1.0%)	2 (0.9%)
PRURITUS	1 (0.9%)	0 (0.0%)	1 (0.5%)
RASH	0 (0.0%)	1 (1.0%)	1 (0.5%)
Urogenital System	1 (0.9%)	0 (0.0%)	1 (0.5%)
URINARY INCONTINENCE	1 (0.9%)	0 (0.0%)	1 (0.5%)

Data Source: Section 15, Source Table 15.4.2.2 and Appendix 16.2, Listings 16.2.4.1.2 and 16.2.4.1.2.1

Non-serious adverse events were counted up to 2 days after last dose; serious adverse events were counted up to 30 days after last dose.

Patients were counted only once at the body system level and at the same preferred term level. Percentages were based on the total number (n) of patients treated in each category.

Study 018: Final Patch Size-ITT-S

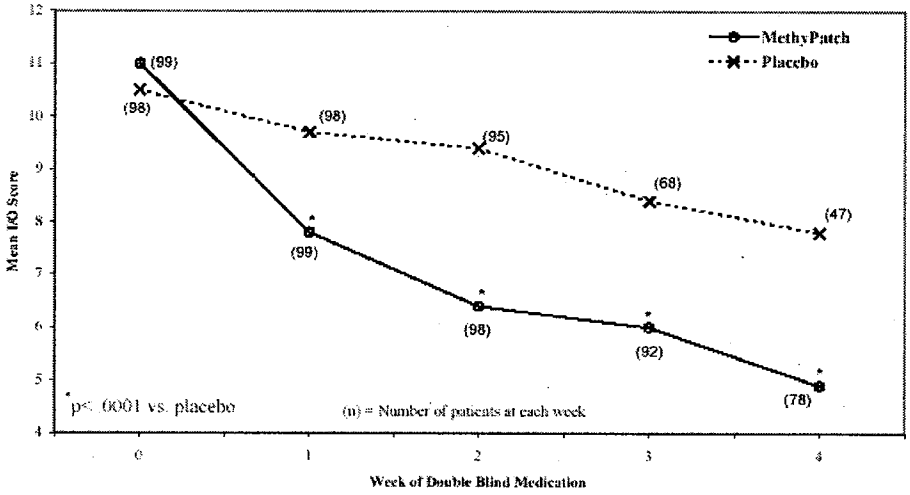
Table 13 Maximum Patch Size and Final Patch Size of Study Medication (cm^2) (ITT-S Population)

	MTS Treatment Group		
Patch Size Statistics	Initial Size 12.50 cm^2 (n= 40)	Initial Size 18.75 cm^2 (n= 66)	Total (n=106)
Maximum Patch Size			
N	40	66	106
12.5 cm^2	2 (5.0%)	0 (0.0%)	2 (1.9%)
18.75 cm^2	3 (7.5%)	13 (19.7%)	16 (15.1%)
25 cm^2	21 (52.5%)	3 (4.5%)	24 (22.6%)
37.5 cm^2	11 (27.5%)	31 (47.0%)	42 (39.6%)
50 cm^2	3 (7.5%)	19 (28.8%)	22 (20.8%)
Final Patch Size			
N	40	66	106
6.25 cm^2	1 (2.5%)	0 (0.0%)	1 (0.9%)
12.5 cm^2	3 (7.5%)	2 (3.0%)	5 (4.7%)
18.75 cm^2	3 (7.5%)	12 (18.2%)	15 (14.2%)
25 cm^2	21 (52.5%)	13 (19.7%)	34 (32.1%)
37.5 cm^2	9 (22.5%)	21 (31.8%)	30 (28.3%)
50 cm^2	3 (7.5%)	18 (27.3%)	21 (19.8%)

Data Source: Section 15, Source Table 15.4.6.2 and Appendix 16.2, Listing 16.2.4.5

Study 018: Mean Teacher I/O Score over Time

Figure 4 Mean Teacher I/O Score Over Time



Study 018: Teacher I/O Change from Baseline by Visit

Table 9 Change From Baseline in Teacher I/O Factor by Visit (ITT-E Population)

Teacher I/O Factor Score	Treatment Group MTS (n=103)	Treatment Group TS (n=104)	Between-Group p-value
Change from Baseline to Visit 3			
N	99	98	
Mean	-3.2	-0.8	
s.d.	3.8	2.7	
Median	-3.0	0.0	
Minimum	-11	-9	
Maximum	5	5	
Within-Group p-value	<0.0001	0.0035	
95% Confidence Interval	-3.9 -2.4	-1.4 -0.3	
LSMEANS	-3.131	-.9554	<0.0001
Change from Baseline to Visit 4			
N	98	95	
Mean	-4.5	-1.3	
s.d.	4.4	2.8	
Median	-4.5	-1.0	
Minimum	-12	-10	
Maximum	5	4	
Within-Group p-value	<0.0001	0.0003	
95% Confidence Interval	-5.4 -3.6	-1.7 -0.5	
LSMEANS	-4.515	-1.231	<0.0001
Change from Baseline to Visit 5			
N	92	68	
Mean	-4.8	-1.3	
s.d.	4.4	3.4	
Median	-4.0	-2.0	
Minimum	-14	-9	
Maximum	7	5	
Within-Group p-value	<0.0001	0.0029	
95% Confidence Interval	-5.7 -3.9	-2.1 -0.4	
LSMEANS	-4.363	-1.485	<0.0001
Change from Baseline to Visit 6			
N	78	47	
Mean	-6.1	-2.0	
s.d.	3.5	3.1	
Median	-6.0	-2.0	
Minimum	-14	-10	
Maximum	0	5	
Within-Group p-value	<0.0001	<0.0001	
95% Confidence Interval	-6.9 -5.3	-2.9 -1.1	
LSMEANS	-5.776	-2.082	<0.0001

Footnotes on second page of 2-page table

Teacher I/O Factor Score	Treatment Group MTS (n=103)	Treatment Group TS (n=104)	Between-Group p-value
Change from Baseline to Visit Final (LOCF)			
N	101	102	
Mean	-5.3	-1.3	
s.d.	4.0	3.2	
Median	-5.0	-1.0	
Minimum	-14	-10	
Maximum	5	5	
Within-Group p-value	<0.0001	0.0006	
95% Confidence Interval	-6.1 -4.5	-1.8 -0.5	
LSMEANS	-5.153	-1.106	<0.0001

Data Source: Section 15, Source Table 15.3.1 and Appendix 16.2, Listing 16.2.3.2

Lower factor scores represent more acceptable behavior. Efficacy was assessed from change from baseline (Change = Post-Baseline Value - Baseline Value). A reduction from baseline (negative change) represents improvement in behavior after treatment.

Within group p-values were derived from paired t-tests and the between-group p-value was derived from the ANCOVA model without interaction term.

Least Squares Means (LSMEANS) change was derived from the ANCOVA model and was the basis for between-group comparison.

Phase III Controlled Studies: Hematology Data

Hematology Data: Baseline, Final and Change from Baseline
Safety Population - Phase III Controlled Pediatric Studies

	MTS	Placebo Only	Total
Basophils (%)			
Baseline			
N	205	212	417
Mean	0.20	0.28	0.24
Standard Deviation	0.31	0.34	0.33
Median	0.10	0.20	0.10
Min - Max	0.0 - 2.0	0.0 - 1.0	0.0 - 2.0
Final			
N	184	183	367
Mean	0.24	0.25	0.24
Standard Deviation	0.32	0.32	0.32
Median	0.10	0.20	0.10
Min - Max	0.0 - 1.0	0.0 - 1.0	0.0 - 1.0
Change From Baseline			
N	184	183	367
Mean	0.04	-0.02	0.01
Standard Deviation	0.40	0.49	0.45
Median	0.00	0.00	0.00
Min - Max	-2.0 - 1.0	-1.0 - 1.0	-2.0 - 1.0
P-Value (1)	0.141	0.498	0.749
(1) The Wilcoxon Signed-Rank Test is used for within patient comparisons of baseline to final.			
Includes Study Number(s): N17-010 and N17-016.			
Eosinophils (%)			
Baseline			
N	205	212	417
Mean	4.34	4.47	4.41
Standard Deviation	3.01	3.45	3.24
Median	3.60	3.00	3.40
Min - Max	0.0 - 18	0.0 - 17	0.0 - 18
Final			
N	184	183	367
Mean	3.80	4.16	3.98
Standard Deviation	2.76	3.05	2.93
Median	3.00	3.70	3.20
Min - Max	0.0 - 20	0.0 - 14	0.0 - 20
Change From Baseline			
N	184	183	367
Mean	-0.59	-0.44	-0.52
Standard Deviation	2.69	3.01	2.85
Median	-0.30	-0.10	-0.20
Min - Max	-8.8 - 7.9	-15 - 8.5	-15 - 8.5
P-Value (1)	0.006	0.059	0.002
Hematocrit (%)			
Baseline			
N	203	209	412
Mean	37.73	37.40	37.56
Standard Deviation	2.30	2.14	2.23
Median	37.70	37.30	37.50
Min - Max	32 - 46	32 - 43	32 - 46
Final			
N	183	177	360
Mean	38.08	37.14	37.62
Standard Deviation	2.55	2.25	2.45
Median	38.20	37.10	37.50
Min - Max	31 - 45	29 - 43	29 - 45
Change From Baseline			
N	183	177	360
Mean	0.42	-0.22	0.11
Standard Deviation	2.20	1.87	2.07
Median	0.40	-0.30	0.20
Min - Max	-10 - 7.7	-6.4 - 4.3	-10 - 7.7
P-Value (1)	0.010	0.147	0.368

	MES	Placebo Only	Total
Hemoglobin (G/DL)			
Baseline			
N	203	209	412
Mean	12.86	12.77	12.81
Standard Deviation	0.77	0.73	0.75
Median	12.90	12.80	12.80
Min - Max	10 - 15	10 - 15	10 - 15
Final			
N	183	177	360
Mean	13.03	12.93	12.98
Standard Deviation	0.88	0.77	0.84
Median	13.10	12.80	12.90
Min - Max	10 - 15	9.3 - 15	9.3 - 15
Change From Baseline			
N	183	177	360
Mean	0.17	-0.02	0.08
Standard Deviation	0.66	0.59	0.63
Median	0.20	0.00	0.10
Min - Max	-2.6 - 2.2	-1.9 - 1.5	-2.6 - 2.2
P-Value (1)	<0.001	0.491	0.021

(1) The Wilcoxon Signed-Rank Test is used for within patient comparisons of Baseline to final.

Includes Study Number(s) M17-010 and M17-018.

Lymphocytes (%)			
Baseline			
N	205	212	417
Mean	38.51	38.14	38.32
Standard Deviation	9.23	9.60	9.41
Median	38.90	37.30	38.00
Min - Max	12 - 62	12 - 66	12 - 66
Final			
N	184	183	367
Mean	37.64	38.06	37.85
Standard Deviation	10.28	10.02	10.13
Median	36.55	37.00	37.00
Min - Max	15 - 75	11 - 96	11 - 96
Change From Baseline			
N	184	183	367
Mean	-0.81	-0.15	-0.48
Standard Deviation	11.07	11.61	11.33
Median	-0.70	0.00	-0.20
Min - Max	-39 - 32	-32 - 64	-39 - 64
P-Value (1)	0.220	0.635	0.227
Monocytes (%)			
Baseline			
N	205	212	417
Mean	5.64	5.76	5.80
Standard Deviation	2.20	2.32	2.26
Median	6.00	5.75	5.90
Min - Max	0.3 - 13	0.0 - 18	0.0 - 18
Final			
N	184	183	367
Mean	5.45	6.05	5.75
Standard Deviation	2.27	2.70	2.51
Median	5.20	6.00	5.90
Min - Max	0.0 - 13	0.0 - 17	0.0 - 17
Change From Baseline			
N	184	183	367
Mean	-0.47	0.30	-0.05
Standard Deviation	2.50	3.34	2.98
Median	-0.15	0.00	0.00
Min - Max	-8.0 - 7.3	-18 - 13	-18 - 13
P-Value (1)	0.014	0.156	0.589

	MTS	Placebo Only	Total
Neutrophils Segs (%)			
Baseline			
N	205	212	417
Mean	51.11	51.36	51.24
Standard Deviation	10.26	10.49	10.36
Median	51.00	51.75	51.40
Min - Max	22 - 82	25 - 77	22 - 82
Final			
N	184	183	367
Mean	52.79	51.49	52.14
Standard Deviation	11.52	10.56	11.06
Median	53.90	52.00	53.00
Min - Max	16 - 79	4.0 - 83	4.0 - 83
Change From Baseline			
N	184	183	367
Mean	1.75	0.23	0.99
Standard Deviation	12.87	12.45	12.67
Median	2.00	0.40	1.00
Min - Max	-35 - 49	-45 - 33	-45 - 49
P-Value (1)	0.027	0.578	0.048

(1) The Wilcoxon Signed-Rank Test is used for within patient comparisons of Baseline to final.

Includes Study Number(s): M17-010 and M17-018.

RBCs (MILL/MCL)			
Baseline			
N	203	209	412
Mean	4.54	4.47	4.51
Standard Deviation	0.33	0.28	0.31
Median	4.50	4.47	4.50
Min - Max	3.8 - 6.1	3.9 - 5.4	3.8 - 6.1
Final			
N	183	177	360
Mean	4.58	4.43	4.51
Standard Deviation	0.34	0.31	0.33
Median	4.57	4.40	4.50
Min - Max	3.6 - 5.4	3.3 - 5.4	3.3 - 5.4
Change From Baseline			
N	183	177	360
Mean	0.05	-0.03	0.01
Standard Deviation	0.24	0.22	0.24
Median	0.05	-0.02	0.00
Min - Max	-1.1 - 0.7	-0.7 - 0.5	-1.1 - 0.7
P-Value (1)	0.004	0.039	0.560
WBCs (THOU/MCL)			
Baseline			
N	203	209	412
Mean	6.94	6.90	6.92
Standard Deviation	1.89	1.81	1.84
Median	6.70	6.80	6.80
Min - Max	3.0 - 12	3.3 - 13	3.0 - 13
Final			
N	183	177	360
Mean	6.98	7.11	7.04
Standard Deviation	1.94	2.00	1.97
Median	6.70	7.00	6.80
Min - Max	2.2 - 14	3.4 - 15	2.2 - 15
Change From Baseline			
N	183	177	360
Mean	0.01	0.17	0.09
Standard Deviation	1.90	2.06	1.98
Median	0.00	0.20	0.10
Min - Max	-5.1 - 5.2	-7.5 - 7.0	-7.5 - 7.0
P-Value (1)	0.888	0.151	0.317

Phase III Controlled Studies: Chemistry Data

	MTS	Placebo Only	Total
ALK Phosphatase (U/L)			
Baseline			
N	204	212	416
Mean	272.80	270.00	271.42
Standard Deviation	83.51	67.96	75.90
Median	260.00	262.00	260.50
Min - Max	63 - 617	68 - 591	63 - 617
Final			
N	186	187	373
Mean	266.37	274.70	270.54
Standard Deviation	80.77	73.22	77.08
Median	249.00	262.00	256.00
Min - Max	109 - 592	155 - 624	109 - 624
Change From Baseline			
N	186	187	373
Mean	-10.22	5.57	-2.30
Standard Deviation	40.48	35.70	38.92
Median	-13.00	4.00	-6.00
Min - Max	-114 - 277	-89 - 213	-114 - 277
P-Value (1)	<0.001	0.059	0.036

(1) The Wilcoxon Signed-Rank Test is used for within patient comparisons of baseline to final.

Includes Study Number(s) N17-010 and N17-015.

Albumin (G/DL)			
Baseline			
N	204	212	416
Mean	4.39	4.41	4.40
Standard Deviation	0.24	0.24	0.24
Median	4.40	4.40	4.40
Min - Max	3.7 - 5.1	3.7 - 5.1	3.7 - 5.1
Final			
N	186	187	373
Mean	4.34	4.33	4.36
Standard Deviation	0.23	0.24	0.24
Median	4.40	4.30	4.40
Min - Max	3.8 - 5.0	3.6 - 5.1	3.6 - 5.1
Change From Baseline			
N	186	187	373
Mean	0.01	-0.09	-0.04
Standard Deviation	0.25	0.22	0.24
Median	0.00	-0.10	0.00
Min - Max	-0.6 - 0.8	-0.7 - 0.6	-0.7 - 0.8
P-Value (1)	0.609	<0.001	0.001
BUN (MG/DL)			
Baseline			
N	204	212	416
Mean	13.59	13.22	13.40
Standard Deviation	3.31	3.26	3.28
Median	13.00	13.00	13.00
Min - Max	6.0 - 23	6.0 - 22	6.0 - 23
Final			
N	186	187	373
Mean	13.91	14.28	14.10
Standard Deviation	3.76	3.64	3.70
Median	14.00	14.00	14.00
Min - Max	7.0 - 26	7.0 - 26	7.0 - 26
Change From Baseline			
N	186	187	373
Mean	0.27	1.02	0.65
Standard Deviation	3.77	3.86	3.83
Median	0.00	1.00	1.00
Min - Max	-11 - 10	-10 - 13	-11 - 13
P-Value (1)	0.275	0.001	0.001

	MTS	Placebo Only	Total
Calcium (MG/DL)			
Baseline			
N	204	212	416
Mean	9.92	9.91	9.91
Standard Deviation	0.40	0.44	0.42
Median	9.90	9.90	9.90
Min - Max	8.9 - 11	8.1 - 12	8.1 - 11
Final			
N	186	187	373
Mean	9.99	9.95	9.97
Standard Deviation	0.44	0.39	0.42
Median	9.90	9.90	9.90
Min - Max	9.0 - 11	9.1 - 11	9.0 - 11
Change From Baseline			
N	186	187	373
Mean	0.08	0.02	0.05
Standard Deviation	0.43	0.42	0.43
Median	0.00	0.00	0.00
Min - Max	-1.3 - 1.3	-1.0 - 2.1	-1.3 - 2.1
P-Value (1)	0.022	0.875	0.081

(1) The Wilcoxon Signed-Rank Test is used for within patient comparisons of baseline to final.

Includes Study Number(s) M17-010 and M17-018.

Chloride (MEQ/L)			
Baseline			
N	204	211	415
Mean	104.00	103.87	103.94
Standard Deviation	1.96	2.02	1.99
Median	104.00	104.00	104.00
Min - Max	97 - 110	98 - 113	97 - 113
Final			
N	186	187	373
Mean	103.62	103.76	103.69
Standard Deviation	2.32	2.37	2.34
Median	104.00	104.00	104.00
Min - Max	98 - 109	97 - 113	97 - 113
Change From Baseline			
N	186	187	373
Mean	-0.34	-0.07	-0.21
Standard Deviation	2.29	2.65	2.48
Median	-1.00	0.00	0.00
Min - Max	-7.0 - 6.0	-12 - 9.0	-12 - 9.0
P-Value (1)	0.064	0.655	0.107
Creatinine (MG/DL)			
Baseline			
N	204	212	416
Mean	0.50	0.51	0.50
Standard Deviation	0.11	0.13	0.12
Median	0.50	0.50	0.50
Min - Max	0.2 - 0.8	0.2 - 1.5	0.2 - 1.5
Final			
N	186	187	373
Mean	0.53	0.51	0.52
Standard Deviation	0.10	0.11	0.11
Median	0.50	0.50	0.50
Min - Max	0.3 - 0.8	0.3 - 0.9	0.3 - 0.9
Change From Baseline			
N	186	187	373
Mean	0.03	0.00	0.02
Standard Deviation	0.09	0.12	0.11
Median	0.00	0.00	0.00
Min - Max	-0.3 - 0.3	-0.6 - 0.4	-0.6 - 0.4
P-Value (1)	<0.001	0.973	0.001

	MTS	Placebo Only	Total
Glucose (MG/DL)			
Baseline			
N	204	212	416
Mean	89.08	91.51	90.32
Standard Deviation	12.57	13.47	13.06
Median	88.00	91.00	89.00
Min - Max	56 - 148	53 - 165	53 - 165
Final			
N	186	187	373
Mean	89.63	89.72	89.68
Standard Deviation	14.91	13.05	13.99
Median	89.00	89.00	89.00
Min - Max	54 - 184	45 - 137	45 - 184
Change From Baseline			
N	186	187	373
Mean	0.10	-1.60	-0.89
Standard Deviation	18.11	16.24	17.20
Median	0.50	-2.00	-1.00
Min - Max	-58 - 97	-63 - 56	-63 - 97
P-Value (1)	0.916	0.143	0.340

(1) The Wilcoxon Signed-Rank Test is used for within patient comparisons of baseline to final.

Includes Study Number(s) N17-010 and N17-018:

Phosphorus (MG/DL)			
Baseline			
N	204	212	416
Mean	4.90	4.89	4.89
Standard Deviation	0.56	0.51	0.53
Median	4.90	4.90	4.90
Min - Max	3.3 - 6.2	2.8 - 6.3	2.8 - 6.3
Final			
N	186	187	373
Mean	4.69	4.99	4.84
Standard Deviation	0.55	0.50	0.54
Median	4.70	5.00	4.90
Min - Max	3.2 - 6.5	3.5 - 6.5	3.2 - 6.5
Change From Baseline			
N	186	187	373
Mean	-0.22	0.11	-0.06
Standard Deviation	0.66	0.63	0.67
Median	-0.20	0.10	-0.10
Min - Max	-1.8 - 1.4	-2.0 - 2.1	-2.0 - 2.1
P-Value (1)	<0.001	0.011	0.188
Potassium (MEQ/L)			
Baseline			
N	204	212	416
Mean	4.33	4.31	4.32
Standard Deviation	0.44	0.41	0.42
Median	4.20	4.20	4.20
Min - Max	3.5 - 5.8	3.5 - 6.0	3.5 - 6.0
Final			
N	186	188	374
Mean	4.29	4.31	4.30
Standard Deviation	0.45	0.39	0.42
Median	4.30	4.20	4.25
Min - Max	3.1 - 5.9	3.5 - 5.9	3.1 - 5.9
Change From Baseline			
N	186	188	374
Mean	-0.04	-0.01	-0.03
Standard Deviation	0.52	0.48	0.50
Median	0.00	0.00	0.00
Min - Max	-1.8 - 1.9	-1.7 - 1.4	-1.8 - 1.9
P-Value (1)	0.127	0.481	0.135

	MTS	Placebo Only	Total
SGOT (AST) (U/L)			
Baseline			
N	204	212	416
Mean	28.50	27.15	27.81
Standard Deviation	15.51	7.82	11.97
Median	27.00	26.00	27.00
Min - Max	3.0 - 228	12 - 63	3.0 - 228
Final			
N	186	187	373
Mean	27.52	27.73	27.62
Standard Deviation	7.97	7.09	7.53
Median	27.00	27.00	27.00
Min - Max	13 - 102	16 - 58	13 - 102
Change From Baseline			
N	186	187	373
Mean	-1.09	0.49	-0.30
Standard Deviation	10.81	6.19	8.83
Median	-1.00	0.00	0.00
Min - Max	-126 - 18	-33 - 29	-126 - 29
P-Value (1)	0.345	0.243	0.847
SGPT (ALT) (U/L)			
Baseline			
N	204	212	416
Mean	19.10	16.71	17.88
Standard Deviation	24.87	7.07	18.15
Median	16.00	15.00	16.00
Min - Max	6.0 - 356	6.0 - 82	6.0 - 356
Final			
N	186	187	373
Mean	16.29	18.45	17.37
Standard Deviation	10.72	10.68	10.70
Median	15.00	17.00	15.00
Min - Max	7.0 - 146	8.0 - 87	7.0 - 146
Change From Baseline			
N	186	187	373
Mean	-3.09	1.66	-0.71
Standard Deviation	16.97	9.01	13.76
Median	-1.00	0.00	0.00
Min - Max	-210 - 17	-14 - 68	-210 - 68
P-Value (1)	<0.001	0.040	0.112

	MTS	Placebo Only	Total
Sodium (MEQ/L)			
Baseline			
N	204	211	415
Mean	142.06	141.86	141.96
Standard Deviation	2.11	2.40	2.26
Median	142.00	142.00	142.00
Min - Max	137 - 149	136 - 150	136 - 150
Final			
N	186	187	373
Mean	142.08	142.07	142.07
Standard Deviation	2.49	2.30	2.39
Median	142.00	142.00	142.00
Min - Max	128 - 149	137 - 156	128 - 156
Change From Baseline			
N	186	187	373
Mean	0.02	0.11	0.06
Standard Deviation	2.79	2.66	2.72
Median	0.00	0.00	0.00
Min - Max	-16 - 7.0	-11 - 11	-16 - 11
P-Value (1)	0.758	0.417	0.422

[illegible]

	MTS	Placebo Only	Total
Total Bilirubin (MG/DL)			
Baseline			
N	204	212	416
Mean	0.36	0.38	0.37
Standard Deviation	0.26	0.21	0.24
Median	0.30	0.30	0.30
Min - Max	0.1 - 2.7	0.1 - 1.7	0.1 - 2.7
Final			
N	186	187	373
Mean	0.37	0.35	0.36
Standard Deviation	0.25	0.21	0.23
Median	0.30	0.30	0.30
Min - Max	0.1 - 1.9	0.1 - 1.6	0.1 - 1.9
Change From Baseline			
N	186	187	373
Mean	0.01	-0.02	-0.01
Standard Deviation	0.17	0.16	0.17
Median	0.00	0.00	0.00
Min - Max	-0.8 - 0.8	-1.1 - 0.7	-1.1 - 0.8
P-Value (1)	0.785	0.274	0.591
Total Cholesterol (MG/DL)			
Baseline			
N	204	212	416
Mean	167.95	167.48	167.67
Standard Deviation	26.98	29.11	28.05
Median	165.00	165.50	165.00
Min - Max	86 - 252	78 - 265	78 - 265
Final			
N	186	187	373
Mean	160.15	164.65	162.42
Standard Deviation	25.66	28.65	27.26
Median	157.50	161.00	161.00
Min - Max	104 - 264	96 - 242	96 - 264
Change From Baseline			
N	186	187	373
Mean	-6.15	-2.81	-4.47
Standard Deviation	19.45	19.60	19.57
Median	-6.00	-2.00	-4.00
Min - Max	-55 - 54	-85 - 45	-85 - 54
P-Value (1)	<0.001	0.033	<0.001
Total Protein (G/DL)			
Baseline			
N	204	212	416
Mean	7.24	7.24	7.24
Standard Deviation	0.40	0.40	0.40
Median	7.20	7.20	7.20
Min - Max	6.2 - 8.6	6.0 - 8.6	6.0 - 8.6
Final			
N	186	187	373
Mean	7.31	7.21	7.26
Standard Deviation	0.42	0.39	0.42
Median	7.30	7.20	7.20
Min - Max	5.8 - 8.4	6.3 - 8.5	5.8 - 8.5
Change From Baseline			
N	186	187	373
Mean	0.08	-0.05	0.02
Standard Deviation	0.39	0.36	0.38
Median	0.05	0.00	0.00
Min - Max	-1.0 - 1.1	-1.0 - 0.9	-1.0 - 1.1
P-Value (1)	0.007	0.105	0.448

	MTS	Placebo Only	Total
Pulse (Beats per Minute)			
Baseline			
N	206	214	420
Mean	84.4	85.1	84.7
Standard Deviation	11.1	12.4	11.8
Median	86.0	86.0	86.0
Min - Max	45 - 120	56 - 123	45 - 123
Final			
N	202	199	401
Mean	88.7	86.0	87.4
Standard Deviation	13.4	11.2	12.4
Median	86.0	86.0	86.0
Min - Max	58 - 132	60 - 115	58 - 132
Change From Baseline			
N	201	199	400
Mean	4.5	1.4	3.0
Standard Deviation	13.4	11.2	12.4
Median	3.0	0.0	2.0
Min - Max	-28 - 48	-36 - 30	-36 - 48
P-Value [1]	<0.001	0.060	<0.001

	MTS	Placebo Only	Total
Body Weight (Kg.)			
Baseline			
N	205	213	418
Mean	33.8	35.2	34.5
Standard Deviation	11.7	12.1	11.9
Median	31.3	32.2	31.8
Min - Max	17 - 93	18 - 80	17 - 93
Final			
N	204	199	403
Mean	33.1	35.8	34.4
Standard Deviation	11.8	12.3	12.1
Median	29.9	32.7	31.3
Min - Max	16 - 89	18 - 81	16 - 89
Change From Baseline			
N	202	199	401
Mean	-0.9	0.5	-0.2
Standard Deviation	1.9	1.3	1.7
Median	-0.9	0.5	0.0
Min - Max	-7 - 17	-5 - 6	-7 - 17
P-Value [1]	<0.001	<0.001	<0.001

Cumulative Duration of MTS Exposure

Text Table 26 Cumulative[1] Duration of Exposure to MTS, n (%)

Safety Population	1-6 days	7-20 days	21-42 days	43-83 days	84-120 days	>120 days	Total
All Pediatric[2]	54 (11)	70 (14)	97 (19)	64 (13)	84 (17)	131 (26)	500
Phase III Controlled[3]	5 (2)	36 (18)	157 (78)	4 (2)	0 (0)	0 (0)	202
Long-Term Pediatric	5 (2)	15 (5)	32 (10)	68 (21)	84 (26)	116 (36)	320
All Adults[3]	117 (57)	89 (43)	0 (0)	0 (0)	0 (0)	0 (0)	206
All Studies	171 (24)	159 (23)	97 (14)	64 (9)	84 (12)	131 (19)	706

1 Exposure to MTS was summed across studies regardless of dose and number of hours worn.

2 Some patients may appear in both the Long-Term Pediatric and Phase III Controlled Pediatric Populations, therefore, data are not additive for the Pediatric Population.

3 Exposure data obtained from the ISS.

Data Source: Tables 4.2 – 4.4 in Section 7.

CLINICAL REVIEW

Appendix

B. Individual More Detailed Study Reviews (If performed)

1. NDA Review, 03/31/03: Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation 1 (DPE1), HFD-860.

2. NDA Statistical Review and Evaluation, 2/14/03: Division of Biometrics I, HFD-710.

3. NDA Clinical Inspection Summary, 01/13/03: Good Clinical Practice Branch II, Division of Scientific Investigations, HFD-47.

4. NDA Consult, HFD-540 #360 (0211074), 03/12/03: Division of Dermatologic and Dental Drug Products, Office of Drug Evaluation V, HFD-540.

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/s/

Glenn Mannheim
4/9/03 12:06:02 PM
MEDICAL OFFICER

Paul Andreason
4/18/03 11:42:45 AM
MEDICAL OFFICER
I agree with Dr Mannheim that the Division should not approve the current [redacted] formulation. See memo to file.