Steady-State Clinical Pharmacokinetics Demonstrating Once-weekly Corplex™ Donepezil Transdermal System as a Therapeutic Alternative to Daily Oral Aricept

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Abstract

- **Background:** Aricept® is approved by the FDA for the treatment of Alzheimer’s disease as a daily tablet. Patient adherence to therapy is poor due to the required daily administration, and gastro-intestinal (GI) adverse effects that may be associated with the oral route of administration. The once-weekly delivery with the donepezil transdermal system using the Corplex technology platform is expected to improve adherence by providing a convenient once-weekly patch, and potentially improve the tolerability profile by bypassing the GI tract. Previously, we have reported positive single-dose pharmacokinetic results with Corplex Donepezil.
- **Methods:** This clinical study is a multiple-dose, randomized crossover study in healthy subjects, with the primary objective of comparing the steady-state plasma concentrations of two different sizes of the transdermal system, targeted to deliver 10 mg/day of donepezil, and the oral Aricept 10 mg after several weeks of treatment. The secondary objectives are assessment of safety and tolerability (including skin tolerability).
- **Results:** Based on the results of our earlier single-dose Phase 1 pharmacokinetic study comparing Corplex Donepezil with oral Aricept, we projected that at steady state, the maximum plasma concentration and the area under the curve of plasma concentration of donepezil with the Corplex Donepezil transdermal system would be similar to the same measurements of oral Aricept. Preliminary, interim steady state data from this study is consistent with our projections. Sustained and controlled delivery of donepezil was demonstrated in the plasma concentrations of all subjects treated with once-weekly Corplex Donepezil for four consecutive weeks. Subjects treated with once-weekly Corplex Donepezil experienced acceptable skin tolerability and no systemic adverse events unique to transdermal delivery.
- **Conclusions:** Sustained and reproducible steady-state pharmacokinetics were demonstrated with the Corplex Donepezil transdermal system, supporting the feasibility of a convenient, safe and effective once-weekly dosing regimen as compared to daily oral administration. A registration pivotal pharmacokinetic is being designed to demonstrate bioequivalence between the once-weekly Corplex patch and oral Aricept at steady-state. Bioequivalence studies are designed to assess the biological equivalence of pharmaceutical products based on their PK profiles. They are relatively short in duration of treatment, and provide a development path that is substantially less costly and more streamlined compared to standard clinical development programs.

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Corplex Platform & Study Design

Corplex Technology Platform

Novel combinations of polymer-based adhesives

Traditional patch
- Poor adhesion
- Excessive drug loading
- Excessive patch sizes
- Skin irritation
- Limited to more soluble drugs

Corplex patch
- Can adhere to wet or dry surfaces
- High efficiency of drug delivery
- More drug delivered per patch area
- Reduced irritation
- Provides access to new drugs

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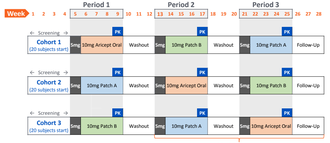
Donepezil Clinical Study: Overall Design

Three period, three-treatment, randomized crossover study



Patch A and Patch B were two different patch sizes of the same formulation
Drug-containing surface area of Patch B was ~20% larger than Patch A
Steady-state PK assessments were made during 0 week of each period*

Actual sequence of final two treatments was randomized

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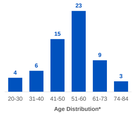
Subject Demographics

- 60 healthy volunteers enrolled at beginning of study
- Very low attrition: 50 completed the study
- >80% were more than 40 years old

Demographic	Distribution
Age	20-78 years
Male/Female	57% / 43%
Non-Hispanic Caucasian/ Hispanic	75% / 25%



*At study initiation

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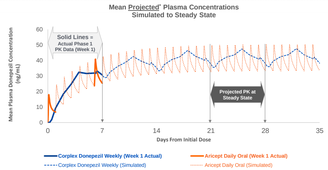
Results and Conclusions

Donepezil Projected Steady State PK Profile



*Projections based on one-week PK study (September 2016, n=6) of Corplex Donepezil and one week PK study (June 2016, n=6) of oral Aricept

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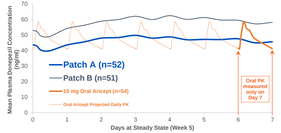
Observed PK Profiles at Steady State

Transdermal Delivery Exhibits Similar PK Profile to Oral Aricept

Patch A and B exhibit dose proportionality



Plasma sampling for patch treatments taken throughout Week 5
Plasma sampling for Aricept taken only on last day (day 7) of Week 5

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Bioequivalence Assessment of Patch A

Patch A is Bioequivalent to Aricept

BE requires the 90% confidence intervals for the geometric mean ratios of AUC_{ss}* and $Cmax_{ss}$ for Patch A vs. Aricept to each be within 80-125%**

Primary PK Parameters	Geometric Mean Ratio (%) (Patch A vs. Oral Aricept)	BE Limits (Target 80-125%)
AUC_{ss} (ng-hr/ml)	104.7	**95.2 - 115.2**
$Cmax_{ss}$ (ng/ml)	91.6	**83.1 - 100.8**

*AUC_{ss} - area under the curve at steady state (for patch, observed area under the curve throughout week 5; for Aricept, observed AUC (day 7 of week 5 multiplied by 7)
**$Cmax_{ss}$ - maximum concentration at steady state (for patch, maximum observed conc. during week 5; for Aricept, maximum observed conc. during day 7 of week 5)

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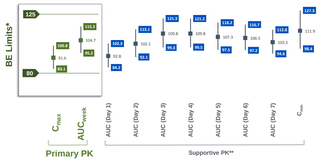
Bioequivalence Assessment (Patch A)



At 90% confidence intervals
The 80 – 125% criteria do not apply to supportive PK parameters; FDA has indicated that these will be tested for “no significant difference” compared to oral Aricept
** % Fluctuation data not shown; as expected, the patch achieved less fluctuation between C_{max} and C_{min} due to controlled delivery*

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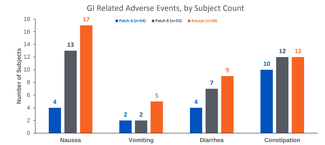
Most Common GI* Side Effects

Patch A incidence of nausea was more than 4x less than Aricept



*GI = Gastrointestinal

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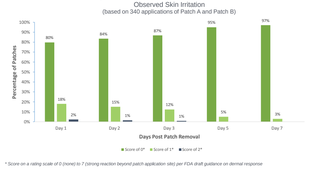
Favorable Skin Tolerability

80% of patches had an irritation score of “0”



* Score on a rating scale of 0 (none) to 7 (strong reaction beyond patch application site) per FDA draft guidance on dermal response

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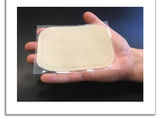
Patch A Wearability: Thin and Flexible

~150cm² Delivers 7 Days of Drug



Thinner Than a Dime

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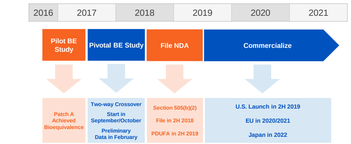
Expected Donepezil Pathway to Commercialization



All years are calendar years

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Key Pilot Study Conclusions

- **Sustained and controlled PK in target age group**
- **Achieved bioequivalence to oral Aricept**
- **Differentiated gastrointestinal adverse event profile**
- **Favorable safety and skin tolerability**
- **Conclusive data to finalize design of pivotal BE study**

Acknowledgements
Corium Team

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