Sustained and Reproducible 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 FDA for the treatment of Alzheimer’s disease as a daily tablet. Patient adherence to therapy is poor due to required daily administration, and gastro-intestinal (GI) adverse effects that may be associated with the oral route of administration. The transdermal delivery of once-weekly Donepezil Transdermal System using the Corplex platform transdermal technology is expected to improve adherence by providing a convenient once-weekly patch, and potentially improve the tolerability profile by bypassing the GI tract.
- **Methods:** This Phase 1 pharmacokinetic (PK) study was conducted in healthy volunteers aged 50 to 80. It was a partial-crossover study with subjects receiving once-weekly Corplex Donepezil Transdermal System and oral Aricept as the comparator. The primary objective was to assess the single dose pharmacokinetics of Corplex Donepezil compared to Aricept. The secondary objectives were assessment of safety and tolerability (including skin tolerability).
- **Results:** Sustained and controlled delivery of donepezil was demonstrated in the plasma concentrations of all subjects treated with once-weekly Corplex Donepezil. The average plasma concentration with Corplex Donepezil was similar to oral Aricept, and indicative of bioequivalence (BE). Pharmacokinetic and statistical projections for subsequent weeks of therapy at steady state predict a highly similar exposure between once-weekly Corplex Donepezil and continued daily oral administration of Aricept. Active metabolite formation was minimal and similar for both the transdermal and oral routes of administration, indicating that there were no changes in metabolite concentration in plasma associated with drug absorption through the skin. Subjects treated with once-weekly Corplex Donepezil experienced acceptable skin tolerability and no systemic adverse events unique to transdermal delivery.
- **Conclusions:** Sustained and reproducible pharmacokinetics were demonstrated with Corplex Donepezil Transdermal System, supporting the feasibility of a convenient, safe and effective once-weekly dosing regimen as compared to daily oral administration. Future pharmacokinetic studies will be designed to demonstrate bioequivalence between the once-weekly Corplex patch and oral Aricept. 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

Corplex Platform Overview

- **Novel polymer blends with hydrophobic and hydrophilic domains**
  - Long term wear and high drug loading capability
    - Hydrophobic domains provide adhesive capability
    - Hydrophilic domains provide capability to hold liquids with solubilized drug
    - Hydrophilic domains provide moisture handling capability
    - Liquid handling capability preserves matrix integrity
- **Proprietary patch design provides**
  - Flexibility
  - Conformability
- **Proprietary formulation provides**
  - Enhanced drug loading
  - Enhanced stability
  - Enhanced delivery

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Corplex Value Proposition

Novel combinations of polymer-based adhesives

Traditional patch	Corplex patch
• Poor adhesion	• Can adhere to wet or dry surfaces
• Excessive drug loading	• High efficiency of drug delivery
• Excessive patch sizes	• More drug delivered per patch area
• Skin irritation	• Reduced irritation
• Limited to more soluble drugs	• Provides access to new drugs

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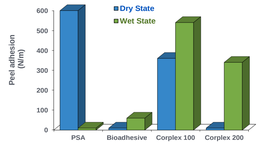
Superior Adhesion

- **Corplex provides adhesion in dry and wet environments**



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Study Design

Phase 1 Clinical Study Overview

- **Open label, randomized, parallel study**
- **Three transdermal treatments**
  - Formulation 1, 2, 3
  - Single-dose, once-weekly patch targeted to deliver 5 mg donepezil per day
  - Plasma sampling during application (Days 1-7) and post removal (Days 8-19)
  - 18 healthy female volunteers; 6 subjects per formulation
- **Lead formulation compared to 5 mg Aricept in a partial cross over study**
  - Six subjects
  - Oral Aricept: administered once daily for 7 days
  - Plasma sampling during Day 1 and on Days 7 through 14

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Phase 1 Clinical Study Overview (cont.)

- **Primary endpoints**
  - Compare PK of three transdermal formulations and select lead formulation
  - Compare PK of lead formulation to oral Aricept 5 mg
    - Focus on 24 hour period on day 7 (represents near steady state conditions)
- **Secondary endpoints**
  - Safety
  - Skin tolerability
- **Steady state simulations**
  - TDS steady-state concentrations projected for Week 4 immediately after four consecutive once-weekly patch applications
    - 10 mg TDS projection based on observed data with patch size scaled for BE
  - 10 mg oral projection based on 5 mg data and assuming dose proportionality

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Eligibility Criteria

- **Key inclusion criteria**
  - Females; 50-80 years of age
  - Body Mass Index (BMI) between 18-32 kg/m^2 (inclusive)
- **Key exclusion criteria**
  - Prior or current use of donepezil hydrochloride or to piperidine derivatives and related drugs within 60 days of dosing
  - History of allergic/hypersensitivity reactions to donepezil or other drugs of the cholinesterase inhibitor class
  - History of allergic reactions to medical grade adhesive tapes, sunscreens, cosmetics, lotions, fragrances, or latex

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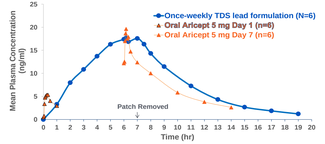
Results and Conclusion

PK Comparable to Oral Aricept

- **Corplex Donepezil achieves plasma concentrations similar to 5 mg Aricept**
- **Patch size can be scaled to achieve 10 mg dose per day**



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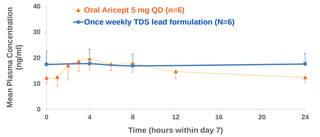
Sustained and Controlled Delivery Demonstrated

- **Sustained PK profile on Day 7**
- **Controlled delivery with minimal peak-to-trough fluctuation**



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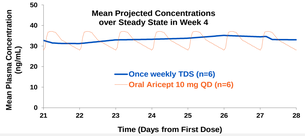
Comparable PK to Oral Projected at Steady State

- **Sustained and controlled delivery at steady state**
- **Corplex Donepezil plasma exposure similar to oral**
  - Supports PK-based bioequivalence for product approval



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Potential Basis for Bioequivalence Approach

- **Geometric Mean Ratio TDS:Oral for PK parameters between 89%-111%**
- **Intra-subject coefficient of variation approximately 20%**
- **Acceptance criteria for bioequivalence (C_{max} and AUC_{week})**
  - 90% confidence intervals within 80%-125% limits
  - Approx. 56 subjects in a two-way crossover study for 80% power
  - Approx. 76 subjects required for 90% power

PK Parameters at Steady State	TDS Once-weekly	Oral Aricept 10 mg QD	Geometric Mean Ratio (TDS:Oral)
Geometric mean C_{max} (ng/ml)	40.6	45.6	0.890
Geometric mean C_{min} (ng/ml)	34.2	30.8	1.110
Geometric mean AUC_{week} (ng-hr/ml)	6367	6165*	1.033

*$AUC_{0\text{-}24\ hours} \times 7\ days$

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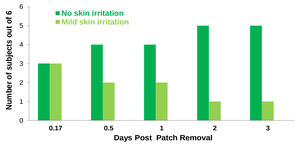
Acceptable Skin Tolerability

- **No to mild irritation demonstrates good skin tolerability**



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Key Phase 1 Conclusions

- **Acceptable safety and skin tolerability**
- **Sustained and controlled PK in target age group (50-80)**
- **Achievement of plasma concentrations similar to oral Aricept**
- **Active metabolite less than 1% of parent and similar to oral Aricept**
- **Steady-state projections show similar donepezil exposure to oral**
  - Supports PK based bioequivalence pathway for approval
  - FDA pre-IND response supports BE based development plans

Acknowledgements
Corium Team

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