What Does the Data from the ATX-101 Phase I Safety and Pharmacokinetic Study Tell Us?

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Minimally invasive submental contouring is an unmet aesthetic need. ATX-101 was developed to address the clinical problem of submental fullness by contouring submental fat. ATX-101 is a patented synthetic formulation of naturally-occurring deoxycholic acid (DCA). DCA is a naturally occurring bodily substance involved in the breakdown of ingested dietary fat. ATX-101 achieves submental contouring when injected into submental fat from a mechanistic standpoint through targeted fat cell death via a process termed focal adipocytolysis. Based upon the safety data, ATX-101 appears to be relatively safe with an associated transient increase of plasma DCA. The most common adverse events of erythema, edema and pain, could be termed "anticipated events" due to the frequency of occurrence and are typical sequela of injection site reactions. Furthermore, these common responses are well aligned with the mechanism of action: localized adipocyte cell death followed by resultant inflammation. Publication of ATX-101 Phase I safety and pharmacokinetic data is an important scientific "look behind the curtain" that provides valuable insight into Phase I clinical trial study design and foundational safety data, while "setting the stage" for future Phase II/III studies that precede arrival of new drugs to market.

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ATX-101, a first-in-class drug, has undergone extensive clinical evaluation to evaluate the safety and efficacy of ATX-101 to reduce submental fullness, with approximately 20 clinical trials involving greater than 2,500 study subjects. These studies include a diverse group of study participants (ages 19-65 and BMI 18-40). Based upon the strength and promise of these clinical trials, a New Drug Application (NDA) was submitted to the U.S. Food and Drug Administration (FDA) in May 2014 and was FDA approved April 29, 2015. It is expected that physician and patient desire for non-surgical methods to reduce submental fat will be addressed with the imminent introduction of ATX-101 (Kybella, Kythera Biopharmaceuticals, Westlake Village, CA) and it is anticipated that ATX-101 will be available for physician use by the second half of 2015.

The article describing the results of the Phase I study examining the safety and pharmacologic properties of ATX-101 titled, "A Phase I Safety and Pharmacokinetic Study of ATX-101: Injectable, Synthetic Deoxycholic Acid for Submental Contouring," was recently published in the *Journal of Drugs and Dermatology*.[1] This article demonstrates the safety and pharmacokinetics of the maximal therapeutic dose of ATX-101 (100 mg total dose) in a cohort of 24 study subjects.

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Study subjects received subcutaneous fifty 0.2 mL depot injections of ATX-101 (2 mg/cm2, with or without 0.9% benzyl alcohol) into the submental fat in a grid-like manner to the submental fat area. All study subjects treated with ATX-101 formulated with or without benzyl alcohol experienced injection site edema (24 of 24 subjects, 100%), nearly all experienced injection site pain (23 of 24 study subjects, 95.8%), and most experienced injection site erythema (20 of 24 subjects, 83.3%). Other common injection site adverse events included injection site anesthesia (66.7%) and hematoma (54.2%). ATX-101 without benzyl alcohol resulted in zero cardiac, eye, musculoskeletal, genitourinary, or gastrointestinal disorders; while ATX-101 benzyl alcohol formulations resulted in cardiac, eye, musculoskeletal, genitourinary, and gastrointestinal disorders. In comparison, ATX-101 formulations with benzyl alcohol resulted in cases of tachycardia (1 of 12 subjects), blepharitis (1 of 12 subjects), ulcerative keratitis (1 of 12 subjects), nausea (3 of 12 subjects), diarrhea (1 of 12 subjects), toothache (1 of 12 subjects), myalgia (1 of 12 subjects), dysuria (1 of 12 subjects), dysgeusia (2 of 12 subjects), and headache (3 of 12 subjects). From this data, it appears that benzyl alcohol-free formulations may result in less ATX-101 side effects and be safer for our patients. Pharmacokinetic data revealed that ATX-101

in benzyl alcohol containing and free formulations were associated with an initial spike in plasma DCA concentrations within one hour that returned to near baseline 24 hours post-treatment. There are limitations associated with this Phase I study, such as small sample size (12 patients per treatment arm), that preclude us from drawing conclusions from the two study groups. Study design incorporating Hanley's Rule of Three[2] may have resulted in greater understanding regarding interpreting adverse events, especially within categories where there were "zero." Additionally, it would have been good to have two additional placebo study arms for purposes of comparison evaluating the benzyl alcohol containing and benzyl alcohol-free formulations without the active ingredient ATX-101. These concerns were addressed in two Phase III clinical trials conducted in Europe[3-5] and two Phase III clinical trials conducted in North America (unpublished data).

Based upon the safety data,[1] ATX-101 appears to be relatively safe with an associated transient increase of plasma DCA. The most common adverse events of erythema, edema and pain, could be termed "anticipated events" due to the frequency of occurrence and are typical sequela of injection site reactions. Furthermore, these common responses are well aligned with the mechanism of action: localized adipocyte cell death followed by resultant inflammation. Publication of ATX-101 Phase I safety and pharmacokinetic data is an important scientific "look behind the curtain" that provides valuable insight into Phase I clinical trial study design and foundational safety data, while "setting the stage" for future Phase II/III studies that precede arrival of new drugs to market. With great enthusiasm I encourage other researchers, pharmaceutical, and device companies to follow suit, and publish Phase I clinical trial results to cultivate and promote research transparency while sharing important safety data.

Disclosure

The author has no financial conflict of interest to declare.

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